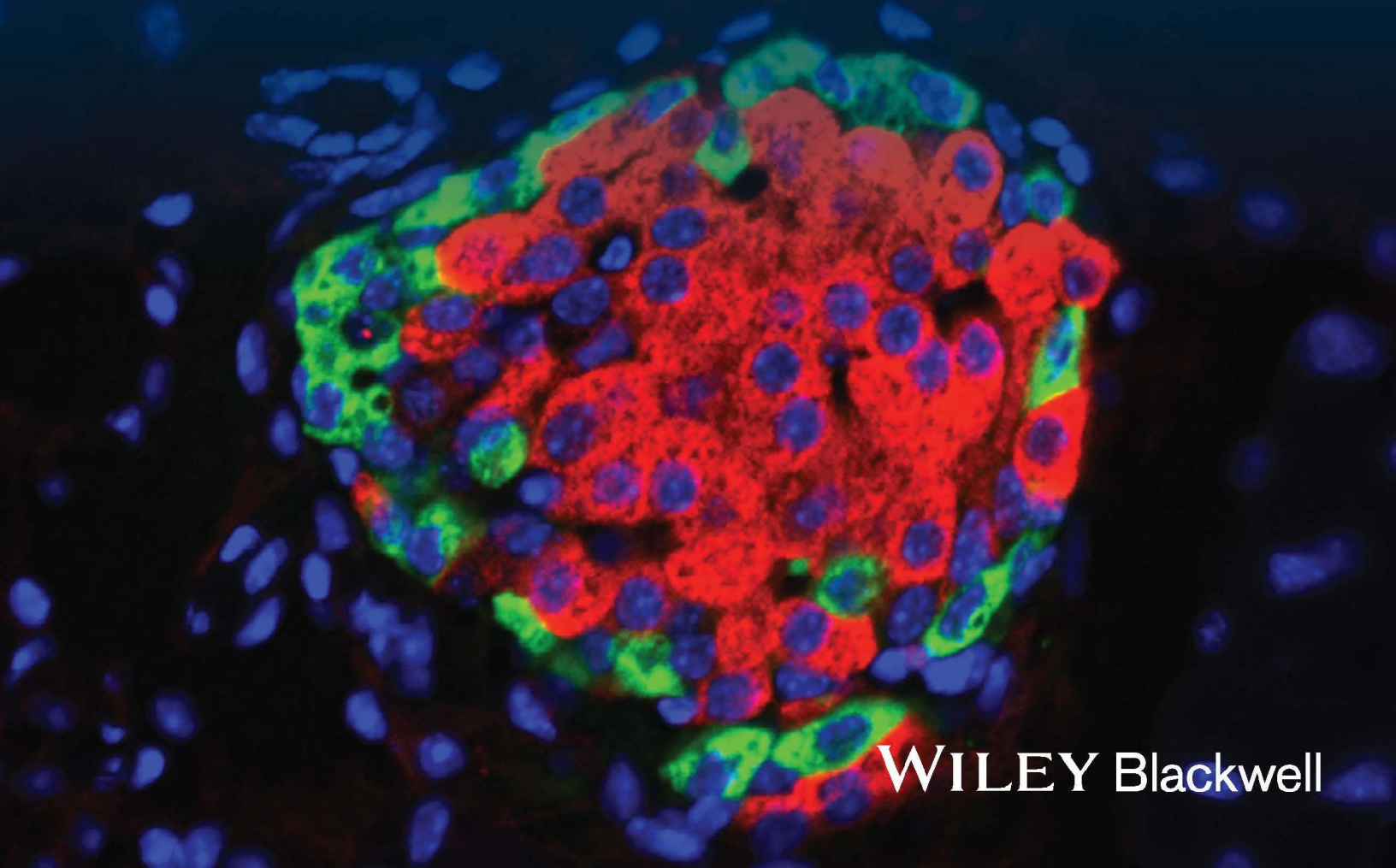
Sixth Edition

Textbook of Diabetes

Edited by Richard I.G. Holt • Allan Flyvbjerg



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We dedicate this book to all people living with diabetes and the healthcare professionals who look after them. We would also like to dedicate this book to our families, without whose support and encouragement the book would never have been finished.

A L G r a w a n y

Textbook of Diabetes

EDITED BY

RICHARD I.G. HOLT MA, MB BChir, PhD, FRCP, FHEA
Professor in Diabetes & Endocrinology
Human Development and Health
Faculty of Medicine, University of Southampton
Southampton, UK
Honorary Consultant Physician
Southampton National Institute for Health Research Biomedical Research Centre
University Hospital Southampton NHS Foundation Trust
Southampton, UK

ALLAN FLYVBJERG MD, DMSc
Former CEO at Steno Diabetes Center Copenhagen (SDCC)
The Capital Region of Denmark
Professor of Clinical Endocrinology
Faculty of Health and Medical Sciences
University of Copenhagen
Copenhagen, Denmark

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Contents

List of Contributors, viii

Preface, xv

List of Abbreviations, xvi

Part 1 Diabetes in its Historical and Social Context

1 The History of Diabetes Mellitus, 3
Robert B. Tattersall and David R. Matthews

2 Classification and Diagnosis of Diabetes, 22
Ambady Ramachandran, Chamukuttan Snehalatha, Arun Raghavan, and Arun Nanditha

3 The Global Burden of Diabetes, 28
Jessica L. Harding, Mary Beth Weber, and Jonathan E. Shaw

4 Epidemiology of Type 1 Diabetes, 41
Lars C. Stene and Jaakko Tuomilehto

5 Epidemiology of Type 2 Diabetes, 55
Ronald C.W. Ma and Peter C.Y. Tong

Part 2 Normal Physiology

6 Overview of Glucose Metabolism, 77
Richard I.G. Holt

7 Islet Function and Insulin Secretion, 84
Peter M. Jones and Shanta J. Persaud

8 Glucagon in Islet and Metabolic Regulation, 99
Jonathan E. Campbell and David A. D'Alessio

9 Mechanism of Insulin Action, 111
Morris F. White

10 Central Control of Glucose Homeostasis, 128
Kimberly M. Alonge, Kendra L. Francis, Nicole E. Richardson, and Michael W. Schwartz

11 Control of Body Weight: How and Why Do We Gain Weight Easier Than We Lose It?, 142
Janine Makaronidis and Rachel L. Batterham

Part 3 Pathogenesis of Diabetes

12 The Genetics of Diabetes, 157
Rashmi B. Prasad

13 Genetics of Obesity, 197
I. Sadaf Farooqi

14 Autoimmune Type 1 Diabetes, 203
Omar Akel and Åke Lernmark

15 Other Disorders with Type 1 Diabetes and Atypical Phenotypes, 216
Alice P.S. Kong, Elaine Y.K. Chow, Andrea O.Y. Luk, and Juliana C.N. Chan

16 Abnormalities of Insulin Secretion and β-Cell Defects in Type 2 Diabetes, 225
Stefano Del Prato, Cristina Bianchi, and Giuseppe Daniele

17 Insulin Resistance in Type 2 Diabetes, 238
Michael Roden, Kitt Falk Petersen, and Gerald I. Shulman

18 Obesity and Diabetes, 250
Nick Finer

19 The Microbiome and Diabetes, 261
Amanda J. Cox, Nicholas P. West, and Allan W. Cripps

Part 4 Other Types of Diabetes

20 Monogenic Causes of Diabetes, 275
Brittany L. Resnick, Maggie H. Shepherd, and Andrew T. Hattersley

21 Drug-Induced Diabetes, 295
Charles D. Ponte and Devra K. Dang

22 Diabetes in Hypersecreting Endocrine Disorders, 304
Allan A. Vaag, Neil A. Hanley, and Caroline M. Kistorp

23 Pancreatic Disease and Diabetes, 319
Ranjit Unnikrishnan and Viswanathan Mohan

24 Clinical Presentations of Diabetes, 330
Ee Lin Lim and Roy Taylor

Part 5 Managing the Person with Diabetes

25 The Aims of Diabetes Care, 343
Katharine D. Barnard-Kelly and Richard I.G. Holt

26 Education to Empower the Person with Diabetes, 354
Ingrid Willaing and Michael Vallis

27 Dietary Management of Diabetes, 368
Nicola Guess

28 Physical Activities and Diabetes, 382
Emma J. Cockcroft and Robert C. Andrews

29 Monitoring Diabetes, 404
Emma English

30 Biomarkers and Precision Medicine in Diabetes, 414
Sok Cin Tye, Michele Provenzano, and Hiddo J.L. Heerspink

Part 6 Treatment of Diabetes

31 Insulin and Insulin Treatment, 431
Roman Vangoitsenhoven, Parth Narendran, and Chantal Mathieu

32 New Technologies for Glucose Monitoring, 444
Thomas Danne and Olga Kordonouri

33 New Technologies for Insulin Administration, 459
Hannah Forde and Pratik Choudhary

34 Whole Pancreas and Islet Cell Transplantation, 473
Braulio A. Marfil-Garza, Peter A. Senior, and A.M. James Shapiro

35 Oral Glucose-Lowering Agents, 492
Clifford J. Bailey and Andrew J. Krentz

36 Non-insulin Parenteral Therapies, 520
Tina Vilsbøll, Mikkel Christensen, Andreas Andersen, and Filip K. Knop

37 How to Use Type 2 Diabetes Treatments in Clinical Practice, 534
Thomas Karagiannis, Aris Liakos, and Apostolos Tsapas

38 Weight Management and Metabolic Surgery, 551
Alexis Sudlow, Dimitri J. Pournaras, and Carel W. le Roux

39 In-Hospital Treatment and Surgery in People with Diabetes, 559
Ketan Dhatariya, Philip Newland-Jones, and Mayank Patel

40 Hypoglycaemia in Diabetes, 579
Ahmed Iqbal, Elaine Y.K. Chow, Timothy W. Jones, and Simon R. Heller

41 Acute Metabolic Complications of Diabetes: Diabetic Ketoacidosis and the Hyperosmolar Hyperglycaemic State in Adults, 602
Philip Newland-Jones, Mayank Patel, and Ketan Dhatariya

Part 7 Microvascular Complications in Diabetes

42 Pathogenesis of Microvascular Complications, 615
Allan Flyvbjerg

43 Diabetic Retinopathy, 629
Toke Bek

44 Diabetic Nephropathy, 640
Peter Rossing and Allan Flyvbjerg

45 Diabetic Neuropathy, 655
Shazli Azmi, Uazman Alam, and Rayaz A. Malik

Part 8 Macrovascular Complications in Diabetes

46 Pathogenesis of Macrovascular Complications in Diabetes, 681
Jakob A. Østergaard, Tomasz J. Block, Sophia Dahm, Waheed Khan, and Karin A.M. Jandeleit-Dahm

47 Hypertension and Diabetes, 700
Peter M. Nilsson

48 Dyslipidaemia and Diabetes, 713
Adie Viljoen, Ahmed Handhle, and Anthony S. Wierzbicki

49 Ischaemic Heart Disease in Diabetes, 724
Michael Lehrke and Nikolaus Marx

50 Heart Failure and Diabetes, 732
Ambarish Pandey, Kershaw V. Patel, and Subodh Verma

51 Cerebrovascular Disease and Diabetes, 745
Colum F. Amory, Jesse Weinberger, and Travis S. Smith

52 Peripheral Vascular Disease, 755
Henrik H. Sillesen

Part 9 Other Complications of Diabetes

53 Foot Problems in People with Diabetes, 771
Frank L. Bowling, Keeley J. Foley, and Andrew J.M. Boulton

54 Sexual Function in Men and Women with Diabetes, 780
Kirsty Winkley, Camilla Kristensen, Jackie Fosbury, and David Price

55 Gastrointestinal Manifestations of Diabetes, 796
Michael Camilleri and Adil E. Bharucha

56 Diabetes and Oral Health, 810
Palle Holmstrup, Christian Damgaard, and Allan Flyvbjerg

57 Diabetes and Non-alcoholic Fatty Liver Disease, 820
Alessandro Mantovani, Giovanni Targher, and Christopher D. Byrne

58 The Skin in Diabetes, 838
Paul Devakar Yesudian

59 Bone and Rheumatic Disorders in Diabetes, 853
Andrew Grey and Nicola Dalbeth

60 Diabetes and Cancer: Risk, Outcomes, and Clinical Implications, 867
Ellena Badrick, Emily J. Gallagher, and Andrew G. Renehan

61 Diabetes and Infections, 878
Andrea O.Y. Luk and Clive S. Cockram

62 Sleep and Diabetes, 897
Sonya Deschênes, Amy McInerney, and Norbert Schmitz

ALGrawany

Part 10 Psychosocial Aspects of Diabetes

63 Psychosocial and Behavioural Aspects of Diabetes, 907
Frans Pouwer and Jane Speight

64 Role of Cognitive Function in Managing People with Diabetes, 922
Tamsin Santos, Chelsea Baird, Sally Eastwood, Kerrie Shiell, and Joseph E. Ibrahim

65 Mental Disorders and Diabetes, 933
Najma Siddiqi, Marietta Stadler, and Richard I.G. Holt

66 Social Aspects of Diabetes, 956
Brian M. Frier and Mark W.J. Strachan

67 Social Determinants of Diabetes, 973
Keri F. Kirk, Gerald McKinley, Briana Mezuk, and Erica Spears

Part 11 Diabetes in Special Groups

68 Ethnic, Cultural, and Religious Aspects to the Management of Diabetes, 987
Wasim Hanif, Sarah N. Ali, and Vinod Patel

69 Diabetes in Childhood, 999
Jennifer M. Ikle, Ananta Addala, and David M. Maahs

70 Adolescence and Emerging Adulthood: Diabetes in Transition, 1019
Charlotte W. Chen and Lori M.B. Laffel

71 Diabetes in Pregnancy, 1034
David R. McCance and Laura Cassidy

72 Diabetes in Old Age, 1072
Ahmed H. Abdelhafiz and Alan J. Sinclair

73 Diabetes at the End of Life, 1085
Trisha Dunning and June James

Part 12 Delivery and Organization of Diabetes Care

74 The Role of the Multidisciplinary Team across Primary and Secondary Care, 1097
Samuel Seidu and Kamlesh Khunti

75 Models of Diabetes Care in Low- and Middle-Income Countries, 1107
David Beran, Sigiriya Aebischer Perone, and Maria Lazo-Porras

Part 13 Future Directions

76 Immunotherapies for Type 1 Diabetes, 1125
Jesper Johannesen and Flemming Pociot

77 Stem Cell Therapy in Diabetes, 1137
Angelo Avogaro and Gian Paolo Fadini

78 Gene Therapy for Diabetes, 1144
Veronica Jimenez and Fatima Bosch

79 Future Drug Treatments for Type 2 Diabetes, 1154
Clifford J. Bailey

Index, 1167

List of Contributors

Ahmed H. Abdelhafiz
Department of Elderly Medicine
Rotherham General Hospital
Rotherham, UK

Ananta Addala
Division of Endocrinology, Department of Pediatrics
Stanford University
Stanford, CA, USA

Omar Akel
Department of Clinical Sciences, Lund University CRC
Skåne University Hospital
Malmö, Sweden

Uazman Alam
Department of Cardiovascular and Metabolic Medicine, Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, UK

Sarah N. Ali
Department of Diabetes and Endocrinology
Royal Free London NHS Foundation Trust
London, UK

Kimberly M. Alonge
UW Medicine Diabetes Institute, Department of Medicine
University of Washington
Seattle, WA, USA

Colum F. Amory
Albany Medical College
Albany, NY, USA

Andreas Andersen
University of Copenhagen
Copenhagen, Denmark

Robert C. Andrews
Faculty of Health & Life Science, Clinical and Biomedical Sciences, University of Exeter, Exeter, UK
Department of Diabetes, Taunton and Somerset NHS Foundation Trust, Taunton, UK

Angelo Avogaro
Department of Medicine
University of Padova
Padua, Italy

Shazli Azmi
Faculty of Biology, Medicine and Health
University of Manchester
Manchester, UK

Ellena Badrick
Division of Cancer Sciences
University of Manchester
Manchester, UK

Clifford J. Bailey
School of Life and Health Sciences
Aston University
Birmingham, UK

Chelsea Baird
Queen Elizabeth Centre, Ballarat Health Service and Department of Forensic Medicine, Monash University
Melbourne, Australia

Katharine D. Barnard-Kelly
Southern Health NHS Foundation Trust
Southampton, UK

Rachel L. Batterham
Centre for Obesity Research, Rayne Institute
Department of Medicine, University College London
University College London Hospital (UCLH)
Bariatric Centre for Weight Management and Metabolic Surgery
National Institute of Health Research, UCLH Biomedical Research Centre
London, UK

Toke Bek
Department of Ophthalmology
Aarhus University Hospital
Department of Clinical Medicine, Faculty of Health
Aarhus University
Aarhus, Denmark

David Beran
Division of Tropical and Humanitarian Medicine
University of Geneva and Geneva University Hospitals
Faculty Diabetes Centre, Faculty of Medicine
University of Geneva
Geneva, Switzerland

Adil E. Bharucha
Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER)
Division of Gastroenterology and Hepatology, Mayo Clinic
Rochester, MN, USA

Cristina Bianchi
Department of Clinical and Experimental Medicine
University of Pisa
Pisa, Italy

Tomasz J. Block
Department of Diabetes, Central Clinical School
Monash University
Melbourne, Australia

Fatima Bosch
Center of Animal Biotechnology and Gene Therapy, Department of Biochemistry and Molecular Biology
University Autònoma de Barcelona
Barcelona, Spain
Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM)
Madrid, Spain

Andrew J.M. Boulton
Department of Medicine, University of Manchester and
Manchester Royal Infirmary
Manchester, UK
Miller School of Medicine
University of Miami
Miami, FL, USA

ALGrawany

Frank L. Bowling
Department of Medicine, University of Manchester and
Manchester Royal Infirmary
Manchester, UK
Miller School of Medicine
University of Miami
Miami, FL, USA

Christopher D. Byrne
Nutrition and Metabolism, Faculty of Medicine
University of Southampton
Southampton National Institute for Health and Care Research Biomedical Research Centre
University Hospital Southampton, Southampton General Hospital
Southampton, UK

Michael Camilleri
Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER)
Division of Gastroenterology and Hepatology, Mayo Clinic
Rochester, MN, USA

Jonathan E. Campbell
Department of Medicine, Division of Endocrinology
Duke University
Durham, NC, USA

Laura Cassidy
Regional Centre for Endocrinology and Diabetes
Royal Victoria Hospital
Belfast, Northern Ireland

Juliana C.N. Chan
Department of Medicine and Therapeutics
Hong Kong Institute of Diabetes and Obesity
Li Ka Shing Institute of Health Sciences
The Chinese University of Hong Kong
Prince of Wales Hospital
Hong Kong, SAR, China

Charlotte W. Chen
Pediatric, Adolescent and Youth Adult Section
Joslin Diabetes Center, and Harvard Medical School
Boston, MA, USA

Pratik Choudhary
Leicester Diabetes Centre
Leicester, UK

Elaine Y.K. Chow
Department of Medicine and Therapeutics
Hong Kong Institute of Diabetes and Obesity
Li Ka Shing Institute of Health Sciences
Phase 1 Clinical Trial Centre
The Chinese University of Hong Kong
Prince of Wales Hospital
Hong Kong, SAR, China

Mikkel Christensen
University of Copenhagen
Copenhagen, Denmark

Emma J. Cockcroft
Faculty of Health & Life Science
Department of Health and Community Sciences
University of Exeter
Exeter, UK

Clive S. Cockram
The Chinese University of Hong Kong
Hong Kong SAR, China

Amanda J. Cox
Menzies Health Institute Queensland and School of Pharmacy and Medical Sciences
Griffith University
Southport, QLD, Australia

Allan W. Cripps
Menzies Health Institute Queensland and School of Medicine
Griffith University
Southport, QLD, Australia

Nicola Dalbeth
Department of Primary Care Health Sciences
University of Oxford
Oxford, UK

David A. D'Alessio
Department of Medicine, Division of Endocrinology
Duke University
Durham, NC, USA

Sophia Dahm
Department of Diabetes, Central Clinical School
Monash University
Melbourne, Victoria, Australia

Christian Damgaard
Department of Odontology, Faculty of Health and Medical Sciences
University of Copenhagen
Copenhagen, Denmark

Devra K. Dang
University of Connecticut School of Pharmacy
Storrs, CT, USA

Giuseppe Daniele
Department of Clinical and Experimental Medicine
University of Pisa
Pisa, Italy

Thomas Danne
Diabetes Center, Children's Hospital AUF DER BULT
Hannover Medical School
Hannover, Germany

Stefano Del Prato
Department of Clinical and Experimental Medicine
University of Pisa
Pisa, Italy

Sonya Deschênes
School of Psychology
University College Dublin
Dublin, Ireland

Ketan Dhatariya
Norfolk and Norwich University Hospitals NHS Foundation Trust
University of East Anglia
Norwich, UK

Trisha Dunning
Formerly of Deakin University
Geelong, Victoria, Australia

Sally Eastwood
Queen Elizabeth Centre, Ballarat Health Service and
Department of Forensic Medicine, Monash University
Melbourne, Australia

Emma English
Faculty of Medicine and Health
University of East Anglia
Department of Clinical Biochemistry
Norfolk and Norwich University Hospital Trust
Norwich, UK

Gian Paolo Fadini
Department of Medicine
University of Padova
Padova, Italy

Sadaf Farooqi
Wellcome-MRC Institute of Metabolic Science
Addenbrooke's Hospital
Cambridge, UK

Nick Finer
National Centre for Cardiovascular Prevention and Outcomes
UCL Institute of Cardiovascular Science
London, UK

Allan Flyvbjerg
Steno Diabetes Center Copenhagen and
Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen
Copenhagen, Denmark

Keeley J. Foley
Department of Medicine, University of Manchester
Manchester Royal Infirmary
Manchester, UK
Miller School of Medicine
University of Miami
Miami, FL, USA

Hannah Forde
Leicester Diabetes Centre
Leicester, UK

Jackie Fosbury
Sussex Community NHS Foundation Trust
Brighton, UK

Kendra L. Francis
UW Medicine Diabetes Institute, Department of Medicine
University of Washington
Seattle, WA, USA

Brian M. Frier
Centre for Cardiovascular Science, The Queen's Medical Research Institute
University of Edinburgh
Edinburgh, UK

Emily J. Gallagher
Division of Endocrinology, Department of Medicine
Icahn School of Medicine at Mount Sinai
New York, NY, USA

Andrew Grey
Department of Medicine
University of Auckland
Auckland, New Zealand

Nicola Guess
Department of Primary Care Health Sciences
University of Oxford
Oxford, UK

Ahmed Handhle
East Hertfordshire Hospitals Trust
Lister Hospital
Stevenage, UK
Department of Clinical Biochemistry
Addenbrooke's Hospital
Cambridge, UK

Wasim Hanif
University Hospitals Birmingham NHS Foundation Trust
Birmingham, UK

Neil A. Hanley
Centre for Endocrinology and Diabetes
University of Manchester
Manchester, UK

Jessica L. Harding
Departments of Medicine and Surgery, School of Medicine
Department of Epidemiology, Rollins School of Public Health
Emory University
Atlanta, GA, USA

Andrew T. Hattersley
Institute of Biomedical and Clinical Science
University of Exeter Medical School
Exeter, UK

Hiddo J.L. Heerspink
Department of Clinical Pharmacy and Pharmacology, University of Groningen
University Medical Center Groningen
Groningen, The Netherlands

Simon R. Heller
Department of Oncology and Metabolism, The Medical School
University of Sheffield
Sheffield, UK

Palle Holmstrup
Department of Odontology, Faculty of Health and Medical Sciences
University of Copenhagen
Copenhagen, Denmark

Richard I.G. Holt
Professor in Diabetes & Endocrinology, Human Development and Health, University of Southampton, Faculty of Medicine and Honorary Consultant Physician, Southampton National Institute for Health Research Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK

Joseph E. Ibrahim
Queen Elizabeth Centre, Ballarat Health Service
Department of Forensic Medicine, Monash University
Melbourne, Australia

Jennifer M. Ikle
Division of Endocrinology, Department of Pediatrics
Stanford University
Stanford, CA, USA

Ahmed Iqbal
Department of Oncology and Metabolism, The Medical School
University of Sheffield
Sheffield, UK

June James
Leicester Diabetes Centre
Leicester, UK

Karin A.M. Jandeleit-Dahm
Department of Diabetes, Central Clinical School
Monash University
Melbourne, Victoria, Australia
German Diabetes Centre (DDZ)
Institute for Clinical Diabetology
Leibniz Centre for Diabetes Research at Heinrich Heine University
Düsseldorf, Germany

Veronica Jimenez
Center of Animal Biotechnology and Gene Therapy, Department of Biochemistry and Molecular Biology
University Autònoma de Barcelona
Barcelona, Spain
Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM)
Madrid, Spain

Jesper Johannesen
Department of Paediatrics and Adolescent Medicine
Herlev and Gentofte Hospital
Steno Diabetes Center Copenhagen
Department of Clinical Medicine, Faculty of Health and Medical Sciences
University of Copenhagen
Copenhagen, Denmark

Peter M. Jones
Department of Diabetes
King's College London
London, UK

Timothy W. Jones
Department of Endocrinology and Diabetes
Perth Children's Hospital and Telethon Kids Institute
Perth, Western Australia, Australia

Thomas Karagiannis
Diabetes Centre and Clinical Research and Evidence-Based Medicine Unit
Second Medical Department, Aristotle University of Thessaloniki
Thessaloniki, Greece

Waheed Khan
Department of Diabetes, Central Clinical School
Monash University
Melbourne, Victoria, Australia

Kamlesh Khunti
Diabetes Research Centre, University of Leicester, Leicester General Hospital, Leicester, UK

Keri F. Kirk
Department of Family Medicine and Psychiatry, Georgetown University School of Medicine
MedStar-Georgetown University Hospital
Washington, DC, USA

Caroline M. Kistorp
Steno Diabetes Center Copenhagen
Rigshospitalet
Copenhagen, Denmark

Filip K. Knop
University of Copenhagen
Copenhagen, Denmark

Alice P.S. Kong
Department of Medicine and Therapeutics
Hong Kong Institute of Diabetes and Obesity
Li Ka Shing Institute of Health Sciences
The Chinese University of Hong Kong
Prince of Wales Hospital
Hong Kong, SAR, China

ALGrawany

Olga Kordonouri
Diabetes Center, Children's Hospital AUF DER BULT
Hannover Medical School
Hannover, Germany

Andrew J. Krentz
Institute for Cardiovascular and Metabolic Research
University of Reading
Reading, UK
Department of Population Health Sciences
King's College London
London, UK

Camilla Kristensen
King's College London
London, UK

Lori M.B. Laffel
Boston Children's Hospital, Division of Endocrinology
Mass General Hospital for Children, Boston and Harvard Medical School
Boston, MA, USA

Maria Lazo-Porras
Division of Tropical and Humanitarian Medicine
University of Geneva
Geneva, Switzerland
CRONICAS Centre of Excellence in Chronic Diseases
Universidad Peruana Cayetano Heredia
Lima, Peru

Michael Lehrke
Department of Internal Medicine I (Cardiology), University Hospital
RWTH Aachen University
Aachen, Germany

Åke Lernmark
Department of Clinical Sciences, Lund University CRC
Skåne University Hospital
Malmö, Sweden

Carel W. le Roux
Diabetes Complications Research Centre
University College Dublin
Dublin, Ireland

Aris Liakos
Diabetes Centre and Clinical Research and Evidence-Based Medicine Unit
Second Medical Department, Aristotle University of Thessaloniki
Thessaloniki, Greece

Ee Lin Lim
Royal Preston Hospital
Preston, UK

Andrea O.Y. Luk
Department of Medicine and Therapeutics
Hong Kong Institute of Diabetes and Obesity
Li Ka Shing Institute of Health Sciences
Phase 1 Clinical Trial Centre
The Chinese University of Hong Kong
Prince of Wales Hospital
Hong Kong, SAR, China

Ronald C.W. Ma
Division of Endocrinology and Diabetes, Department of Medicine and Therapeutics
Li Ka Shing Institute of Health Sciences
Hong Kong Institute of Diabetes and Obesity
The Chinese University of Hong Kong
Prince of Wales Hospital
Hong Kong, SAR, China

David M. Maahs
Division of Endocrinology, Department of Pediatrics
Stanford University
Stanford, CA, USA

Janine Makaronidis
Centre for Obesity Research, Rayne Institute
Department of Medicine, University College London
University College London Hospital (UCLH)
Bariatric Centre for Weight Management and Metabolic Surgery
National Institute of Health Research, UCLH Biomedical Research Centre
London, UK

Rayaz A. Malik
Department of Medicine
Weill Cornell Medicine-Qatar
Doha, Qatar

Alessandro Mantovani
Section of Endocrinology, Diabetes and Metabolism, Department of Medicine
University of Verona
Verona, Italy

Braulio A. Marfil-Garza
Department of Surgery
University of Alberta
Edmonton, Alberta, Canada

Nikolaus Marx
Department of Internal Medicine I (Cardiology), University Hospital
RWTH Aachen University
Aachen, Germany

Chantal Mathieu
Clinical and Experimental Endocrinology, Department of Chronic Diseases and Metabolism
KU Leuven and University Hospitals
Leuven, Belgium

David R. Matthews
University of Oxford
Oxford, UK

David R. McCance
Regional Centre for Endocrinology and Diabetes
Royal Victoria Hospital
Belfast, Northern Ireland

Dayna E. McGill
Boston Children's Hospital, Division of Endocrinology
Mass General Hospital for Children, Boston and Harvard Medical School
Boston, MA, USA

Amy McInerney
School of Psychology
University College Dublin
Dublin, Ireland

Gerald McKinley
Department of Pathology and Laboratory Medicine, Schulich Interfaculty Program in Public Health
Schulich School of Medicine and Dentistry, Western University
London, ON, Canada

Briana Mezuk
Center for Social Epidemiology and Population Health
University of Michigan School of Public Health
Ann Arbor, MI, USA

Viswanathan Mohan
Dr. Mohan's Diabetes Specialities Centre
IDF Centre of Excellence in Diabetes Care
Madras Diabetes Research Foundation
ICMR Center for Advanced Research on Diabetes
Chennai, India

Arun Nanditha
Dr. A. Ramachandran's Diabetes Hospitals
India Diabetes Research Foundation
Chennai, India

Parth Narendran
Institute of Biomedical Research, The Medical School
University of Birmingham and The Queen Elizabeth Hospital
Birmingham, UK

Philip Newland-Jones
University Hospitals Southampton NHS Foundation Trust
Southampton, UK

Peter M. Nilsson
Lund University
Skåne University Hospital
Malmö, Sweden

Jakob A. Østergaard
Department of Diabetes, Central Clinical School
Monash University
Melbourne, Victoria, Australia
Steno Diabetes Center
Aarhus and Department of Endocrinology &
Internal Medicine, Aarhus University Hospital
Aarhus, Denmark

Ambarish Pandey
Division of Cardiology, Department of Internal Medicine
UT Southwestern Medical Center
Dallas, TX, USA

Kershaw V. Patel
Department of Cardiology
Houston Methodist DeBakey Heart and Vascular Center
Houston, Texas, USA

Mayank Patel
University Hospitals Southampton NHS Foundation Trust
Southampton, UK

Vinod Patel
Warwick Medical School
University of Warwick
Coventry, UK
Acute Medicine, Medical Obstetrics, Diabetes and Endocrinology Centre, George Eliot Hospital NHS Trust, Nuneaton, UK

Sigiriya Aebischer Perone
Division of Tropical and Humanitarian Medicine
Geneva University Hospitals
Geneva, Switzerland

Shanta J. Persaud
Department of Diabetes
King's College London
London, UK

Kitt Falk Petersen
Department of Internal Medicine and Yale Diabetes Research Center
Yale School of Medicine
New Haven, CT, USA

Flemming Pociot
Steno Diabetes Center Copenhagen
Department of Clinical Medicine, Faculty of Health and Medical Sciences
University of Copenhagen
Copenhagen, Denmark

Charles D. Ponte
Robert C. Byrd Health Sciences Center, West Virginia University – Schools of Pharmacy and Medicine, One Medical Center Drive, Morgantown, WV, USA

Dimitri J. Pournaras
Department of Bariatric Surgery
Southmead Hospital
Bristol, UK

Frans Pouwer
Department of Psychology, University of Southern Denmark and
Steno Diabetes Center Odense (SDCO)
Odense, Denmark
School of Psychology, Deakin University
Geelong, Victoria, Australia

Rashmi B. Prasad
Lund University Diabetes Centre, Department of Clinical Sciences, Diabetes and Endocrinology, Lund University
Malmö, Sweden
Institute for Molecular Medicine Finland (FIMM)
Helsinki University
Helsinki, Finland

David Price
Morriston Hospital
Swansea, UK

Michele Provenzano
Nephrology, Dialysis and Renal Transplant Unit
S'Orsola Hospital - IRCCS - Alma Mater Studiorum
University of Bologna, Italy

Arun Raghavan
Dr. A. Ramachandran's Diabetes Hospitals
India Diabetes Research Foundation
Chennai, India

Ambady Ramachandran
Dr. A. Ramachandran's Diabetes Hospitals
India Diabetes Research Foundation
Chennai, India

Andrew G. Renehan
Division of Cancer Sciences
University of Manchester
Manchester, UK

Brittany L. Resnick
Exeter NIHR Clinical Research Facility
Royal Devon University Healthcare NHS Foundation Trust
Exeter, UK

Nicole E. Richardson
UW Medicine Diabetes Institute,
Department of Medicine
University of Washington
Seattle, WA, USA

Michael Roden
Department of Endocrinology and Diabetology,
Medical Faculty and University Hospital
Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research
Heinrich-Heine University Düsseldorf
Düsseldorf, Germany
German Center for Diabetes Research,
Partner Düsseldorf
München-Neuherberg, Germany

Peter Rossing
Steno Diabetes Center Copenhagen
Department of Clinical Medicine,
Faculty of Health and Medical Sciences
University of Copenhagen
Copenhagen, Denmark

Tamsin Santos
Queen Elizabeth Centre, Ballarat Health Service and
Department of Forensic Medicine,
Monash University
Melbourne, VIC, Australia

Norbert Schmitz
Department of Psychiatry, McGill University
Douglas Mental Health University Institute
Montreal, Canada
Department of Population-Based Medicine
University of Tübingen
Tübingen, Germany

Michael W. Schwartz
UW Medicine Diabetes Institute,
Department of Medicine
University of Washington
Seattle, WA, USA

Samuel Seidu
Diabetes Research Centre
University of Leicester, Leicester General Hospital
Leicester, UK

Peter A. Senior
Department of Medicine and Clinical Islet Transplant Program
University of Alberta
Edmonton, Alberta, Canada

A.M. James Shapiro
Department of Medicine
University of Alberta
Edmonton, Alberta, Canada

ALGrawany

Jonathan E. Shaw
Clinical and Population Health, Baker Institute
School of Life Sciences, La Trobe University
School of Public Health and Preventive Medicine, Monash University
Melbourne, Australia

Maggie H. Shepherd
Exeter NIHR Clinical Research Facility,
Royal Devon and Exeter NHS Foundation Trust
Institute of Biomedical and Clinical Science, University of Exeter Medical School
Exeter, UK

Kerrie Shiell
Queen Elizabeth Centre, Ballarat Health Service
Department of Forensic Medicine, Monash University
Melbourne, Australia

Gerald I. Shulman
Departments of Internal Medicine and Cellular & Molecular Physiology, and Yale Diabetes Research Center
Yale School of Medicine
New Haven, CT, USA

Najma Siddiqi
Department of Health Sciences
University of York and Hull York Medical School
York, UK
Bradford District Care NHS Foundation Trust
Bradford, UK

Henrik H. Sillesen
Department of Vascular Surgery, Rigshospitalet
University of Copenhagen
Copenhagen, Denmark

Alan J. Sinclair
Foundation for Diabetes Research in Older People (DROP)
King's College London
London, UK

Travis S. Smith
Albany Medical College
Albany, NY, USA

Chamukuttan Snehalatha
Dr. A. Ramachandran's Diabetes Hospitals
India Diabetes Research Foundation
Chennai, India

Erica Spears
Louisiana Public Health Institute
New Orleans, LA, USA

Jane Speight
Department of Psychology, University of Southern Denmark, Odense, Denmark
Department of Medical Psychology
Amsterdam UMC, Amsterdam, The Netherlands
Australian Centre for Behavioural Research in Diabetes, Diabetes Victoria
Melbourne, Victoria, Australia

Marietta Stadler
Department of Diabetes, School of Cardiovascular and Metabolic Medicine and Sciences
Faculty of Live Sciences and Medicine
King's College London
London, UK

Lars C. Stene
Department of Chronic Diseases, Norwegian Institute of Public Health
Oslo Diabetes Research Centre, Oslo University Hospital
Oslo, Norway

Mark W.J. Strachan
Metabolic Unit
Western General Hospital
Edinburgh, UK

Alexis Sudlow
Department of Bariatric Surgery
Southmead Hospital
Bristol, UK

Giovanni Targher
Section of Endocrinology, Diabetes and Metabolism, Department of Medicine
University of Verona
Verona, Italy

Robert B. Tattersall
University of Nottingham
Nottingham, UK

Roy Taylor
Diabetes Research Group, Institute of Translational and Clinical Research
Newcastle University
Newcastle upon Tyne, UK

Peter C.Y. Tong
The Jockey Club School of Public Health and Primary Care
The Chinese University of Hong Kong
Hong Kong SAR, China

Apostolos Tsapas
Diabetes Centre and Clinical Research and Evidence-Based Medicine Unit
Second Medical Department, Aristotle University of Thessaloniki
Thessaloniki, Greece
Harris Manchester College
University of Oxford
Oxford, UK

Jaakko Tuomilehto
Department of Public Health, University of Helsinki
Helsinki, Finland
National School of Public Health
Madrid, Spain
Diabetes Research Group, King Abdulaziz University
Jeddah, Saudi Arabia

Sok Cin Tye
Department of Clinical Pharmacy and Pharmacology, University of Groningen
University Medical Center Groningen
Groningen, The Netherlands

Ranjit Unnikrishnan
Dr. Mohan's Diabetes Specialities Centre
IDF Centre of Excellence in Diabetes Care
Madras Diabetes Research Foundation
ICMR Center for Advanced Research on Diabetes
Chennai, India

Allan A. Vaag
Steno Diabetes Center Copenhagen
Rigshospitalet
Copenhagen, Denmark

Michael Vallis
Department of Family Medicine
Dalhousie University
Halifax, NS, Canada

Roman Vangoitsenhoven
Clinical and Experimental Endocrinology, Department of Chronic Diseases and Metabolism
KU Leuven and University Hospitals
Leuven, Belgium

Subodh Verma
Division of Cardiac Surgery, St Michael's Hospital
University of Toronto
Toronto, ON, Canada

Adie Viljoen
East Hertfordshire Hospitals Trust
Lister Hospital
Stevenage, UK
Department of Clinical Biochemistry
Addenbrooke's Hospital
Cambridge, UK

Tina Vilsbøll
University of Copenhagen
Copenhagen, Denmark

Mary Beth Weber
Global Diabetes Research Center and Hubert
Department of Global Health
Rollins School of Public Health
Emory University
Atlanta, GA, USA

Jesse Weinberger
Mount Sinai School of Medicine
New York, NY, USA

Nicholas P. West
Menzies Health Institute Queensland
and School of Pharmacy and Medical Sciences
Griffith University
Southport, QLD, Australia

Morris F. White
Division of Endocrinology, Children's Hospital Boston
Harvard Medical School
Boston, MA, USA

Anthony S. Wierzbicki
Guy's & St Thomas Hospitals
London, UK

Ingrid Willaing
Steno Diabetes Center Copenhagan
Copenhagen, Denmark and Department of Health
Services Research, Institute of Public Health
University of Copenhagen
Copenhagen, Denmark

Kirsty Winkley
King's College London
London, UK

Paul Devakar Yesudian
Department of Dermatology,
Wrexham Maelor Hospital
Betsi Cadwaladr University Health Board
Wrexham, UK

A L G r a w a n y

Preface

It is nearly seven years since the last edition of the *Textbook of Diabetes* was published, during which time there have been many exciting developments in our understanding of diabetes and novel treatments that have improved the lives of those living with diabetes. Despite our ability to alleviate the risk of its long-term complications, the global burden of diabetes continues to rise as the prevalence inexorably increases. According to the International Diabetes Federation, diabetes now affects 537 million adults, compared with 415 million when the last edition was published. Over three-quarters of people with diabetes live in low- and middle-income countries and diabetes causes 6.7 million deaths a year, approximately one every five seconds. The cost of treating diabetes has reached almost US$1 trillion per annum, a threefold increase over the last 15 years. The need for accurate and up-to-date information to help healthcare professionals support people with diabetes has never been greater.

Ironically, as the volume of information and diversity of digital resources have increased, many are finding it overwhelming to keep abreast of the new advances. It is particularly challenging to determine the validity of many source materials. In this textbook we aim to bring together a series of chapters from internationally leading diabetes experts who provide accurate and clinically relevant information to both academic and practising diabetes healthcare professionals.

We have retained the structure from the previous edition, with a similar length and number of chapters. The centenary of the discovery of insulin has just passed and the book begins with a history of diabetes that provides many valuable insights from the past. We then move through the epidemiology of diabetes, the physiology of glucose metabolism, and the pathogenesis of diabetes, before sections on clinical management. A discussion of the microvascular and macrovascular complications then follows, after which there are sections on the psychosocial aspects of diabetes, the management of diabetes in special groups, and models of care, before a final section to glimpse into the future. New chapters include an overview of glucose homeostasis and the central control of glucose metabolism, as well as chapters on the genetics and management of obesity to recognize the close relationship between obesity and type 2 diabetes. There is a new chapter on the emerging topic of biomarkers and precision medicine, while the rapid advance in diabetes technology has necessitated a split into separate chapters on glucose monitoring and insulin delivery. Transplantation has moved from future treatments to current management to acknowledge its current place in clinical care. In the macrovascular section, we have added a new chapter on heart failure, which has come to the fore as a result of the sodium–glucose cotransporter 2 (SGLT-2) inhibitor cardiovascular outcome trials. Oral health and sleep are added to the list of other areas of diabetes complications, while the importance of social determinants of health and ethnicity, culture, and religion is now included in the psychosocial aspects of diabetes section. The final new chapter describes managing diabetes in low- to middle-income countries, where the majority of people with diabetes live.

As editors, we are only too aware of the hard work that goes into the production of a comprehensive and up-to-date book such as this. For this edition the pressures of the Covid-19 pandemic added to the challenges of bringing the book to fruition. Our thanks go to each and every chapter author who, despite busy academic, clinical, and professional lives, was prepared to devote the time, energy, and expertise to provide their essential contributions to the text. Thank you for your forbearance of our nagging e-mails!

We are also grateful for the support we have received from our publisher, Wiley-Blackwell. Our commissioning editor Jennifer Seward, who took over from Priyanka Gibbons during the book's development, has provided guidance and encouragement. Our thanks also go to Rajalaxmi Rajendrasingh, Sally Osborn, and the rest of the Wiley-Blackwell team. The book looks even better than the last edition! We would like to pay tribute to Clive Cockram and Barry Goldstein, our editing colleagues for the fourth and fifth editions. You were missed this time round.

We hope you enjoy reading the book, whether it be dipping in or reading from cover to cover, as much as we did editing it. We have taken away useful, novel information that will aid in our daily professional lives and hope that this book will help you to support the people with diabetes you know in the widest sense of this meaning.

Richard I.G. Holt
Allan Flyvbjerg
February 2023

List of Abbreviations

AACE	American Association of Clinical Endocrinologists
AAV	adeno-associated vectors
ABP	ankle blood pressure
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	angiotensin-converting enzyme
ACHOIS	Australian Carbohydrate Intolerance Study in Pregnant Women
ACR	albumin : creatinine ratio
ADA	American Diabetes Association
ADP	adenosine diphosphate
AICAR	5-aminoimidazole-4-carboxamide-1β-D-ribofuranoside
AMDCC	Animal Models for Diabetes Complications Consortium
AMP	adenosine monophosphate
Apo	apolipoprotein
aPWV	aortic pulse wave velocity
Arx	aristaless-related homeobox
ATP	adenosine triphosphate
AUC	area under the curve
BCAA	branched-chain amino acid
BMD	bone mineral density
BMI	body mass index
BM-MNC	mononuclear bone marrow-derived stem cell
BPH	benign prostatic hyperplasia
bpm	beats per minute
BTX-A	botulinum toxin type A
CABG	coronary artery bypass grafting
CA-MRSA	community-associated methicillin-resistant *Staphylococcus aureus*
CAPD	continuous ambulatory peritoneal dialysis
CBG	capillary blood glucose
CBT	cognitive–behavioral therapy
CCM	corneal confocal microscopy
CDA	Canadian Diabetes Association
CDC	cardiosphere-derived stem cell
CDC	Centers for Disease Control and Prevention
CDE	Certified Diabetes Educator
CEMACH	Confidential Enquiry into Maternal and Child Health
CETP	cholesteryl ester transfer protein
CGM	continuous glucose monitoring
CI	confidence interval
CKD	chronic kidney disease
CML	carboxymethyllysine
CNS	central nervous system
COC	combination oral contraceptive
COX	cyclooxygenase
CPC	cardiac progenitor cell
CRP	C-reactive protein
CSII	continuous subcutaneous insulin infusion
CT	computed tomography
CV	coefficient of variation
CVD	cardiovascular disease
DAWN	Diabetes Attitudes, Wishes, and Needs study
DCCT	Diabetes Control and Complications Trial
DKA	diabetic ketoacidosis
DPP	dipeptidyl peptidase
DSN	diabetes specialist nurse
DVLA	Driver and Vehicle Licensing Agency
EASD	European Association for the Study of Diabetes
ECG	electrocardiography/electrocardiogram
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ER	endoplasmic reticulum
ERCP	endoscopic retrograde cholangiopancreatography
ERK	extracellular signal-regulated kinase
ERM	ezrin–radixin–moesin
ESC	embryonic stem cell
ESRD	end-stage renal disease
ESRF	end-stage renal failure
FDA	Food and Drug Administration (USA)
FDC	fixed-dose combination
FDKP	fumaryldiketopiperazine
FFA	free fatty acid
FGF	fibroblast growth factor
FHWA	Federal Highways Administration
FMD	flow-mediated endothelium-dependent arterial dilation
FOXO	forkhead box O
FXR	farnesoid-X receptor
G6P	glucose-6-phosphatase
G-6-P	glucose-6-phosphate
G6PD	glucose-6-phosphate dehydrogenase
GAD	glutamine acid decarboxylase
GCGR	glucagon receptor
GCK	glucokinase
G-CSF	granulocyte colony-stimulating factor

ALGrawany

GDF	growth differentiation factor
GDM	gestational diabetes mellitus
CF	cystic fibrosis
GI	gastrointestinal
GLO	glyoxalase
GLP-1RA	GLP-1 receptor agonist
GLUT	glucose transporter
GPR	G-protein-coupled receptor
GRPP	glicentin-related pancreatic polypeptide
GWA	genome-wide association
GWAS	genome-wide association studies
HAPO	Hyperglycemia and Adverse Pregnancy Outcomes
HbA_{1c}	hemoglobin A_{1c}
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HGF	hepatocyte growth factor
hGH	human recombinant growth hormone
HHS	hyperosmolar non-ketotic hyperglycemic state
HR	hazard ratio
HRT	hormone replacement therapy
HRV	heart rate variability
HSC	hematopoietic stem cell
hsCRP	high-sensitivity C-reactive protein
IADPSG	International Association of Diabetes Pregnancy Study Groups
IAsp	insulin aspart
IAUC	incremental area under the blood glucose curve
ICA	islet cell antibody
ICU	intensive care unit
i.d.	intradermal
IDDM	insulin-dependent diabetes mellitus
IDeg	insulin degludec
IDF	International Diabetes Federation
IDL	intermediate-density lipoprotein
IDRS	Indian Diabetes Risk Score
IgG	immunoglobulin G
IGR	impaired glucose regulation
IGT	impaired glucose tolerance
IKKβ	inhibitor κB kinase-β
IL	interleukin
IMT	intima-media thickness
InsR	insulin receptor
IRMA	intraretinal microvascular abnormality
ISPAD	International Society for Pediatric and Adolescent Diabetes
IT	information technology
IVUS	intravascular ultrasound
IWGDF	International Working Group on the Diabetic Foot
JBDS	Joint British Diabetes Societies
KDIGO	Kidney Disease: Improving Global Outcomes
K_m	Michaelis constant
LADA	latent autoimmune diabetes in adults
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LDLR	low-density lipoprotein receptor
LGA	large-for-gestational age
LIRKO	liver-specific InsR knockout
LPS	lipopolysaccharide
Lst	limostatin
LV	left ventricular
LVEF	left ventricular ejection fraction
MAOI	monoamine oxidase inhibitor
MDI	multiple daily injection
MDRD	Modification of Diet in Renal Disease
MG53	mitsugumin 53
mGDP	mitochondrial glycerolphosphate dehydrogenase
MGO	methylglyoxal
MI	myocardial infarction
MIBG	*m*-iodobenzylguanidine
MIRKO	muscle-specific InsR knockout
MODY	maturity-onset diabetes of the young
MPGF	major proglucagon fragment
MPO	myeloperoxidase
MRI	magnetic resonance imaging
MSC	mesenchymal stem cell
MS	mass spectrometry
mTOR	mammalian or mechanistic target of rapamycin
mTORC1	mechanistic target of rapamycin complex 1
MTPI	microsomal transfer protein inhibitor
NAD	nicotinamide adenine dinucleotide
NaDIA	National Diabetes Inpatient Audit
NAFLD	non-alcoholic fatty liver disease
NANC	non-adrenergic, non-cholinergic
NCV	nerve conduction velocity
NEFA	non-esterified fatty acid
MFMU	Maternal–Fetal Medicine Units Network
NEP	neutral endopeptidase
NFκB	nuclear factor κB
Ngn3	neurogenin 3
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIDDM	non-insulin-dependent diabetes mellitus
NIH	National Institutes of Health
NMU	neuromedin U
Nox	NAD(P)H oxidase
NOD	non-obese diabetic
NPH	neutral protamine Hagedorn
NRTI	nucleoside reverse-transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug
NT-3	neurotrophin-3
NT-proBNP	N-terminal pro-brain-type natriuretic peptide
OCP	oral contraceptive pill
OGIS	oral glucose insulin sensitivity
OGTT	oral glucose tolerance test(ing)
OR	odds ratio
oxLDL	oxidation of low-density lipoprotein
PAS	periodic acid–Schiff
PBA	phenylboronic acid
PC	prohormone convertase
PCB	polychlorinated biphenyl
PCI	percutaneous coronary intervention
PCR	polymerase chain reaction
PCSK-9	proprotein convertase subtilisin kexin type 9
PDH	pyruvate dehydrogenase
Pdx1	pancreatic duodenal homeobox 1
PGF	placental growth factor
PI	protease inhibitor

PI3K	phosphatidylinositol 3-kinase
PID	proportional integral derivative
P/KX	combined pancreas/kidney transplantation
PNDM	permanent neonatal diabetes mellitus
PPAR	peroxisome proliferator-activated receptor
PROactive	Prospective Pioglitazone Clinical Trial in Macrovascular Events
PTDM	post-transplantation diabetes mellitus
PTP1B	protein tyrosine phosphatase 1B
PYY	polypeptide YY
QoL	quality of life
RA	receptor agonist
RAMP	receptor activity-modifying protein
RCT	randomized controlled trial
RDN	renal denervation
RECORD	Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes
REMS	Risk Evaluation and Mitigation Strategy
rHuPH20	recombinant human hyaluronidase
RMR	resting metabolic rate
ROS	reactive oxygen species
RR	relative risk
RR	risk ratio
RT-PCR	reverse transcriptase polymerase chain reaction
SCFA	short-chain fatty acid
s.c.	subcutaneous
sdHDL	small, dense high-density lipoprotein
sdLDL	small, dense low-density lipoprotein
SDS-PAGE	sodium dodecyl sulfate polyacrylamide gel electrophoresis
SGA	second-generation antipsychotics
SHP	short heterodimer protein
SMBG	self-monitoring of blood glucose
SMI	severe mental illness
SNP	sub-basal nerve plexus
SSRI	selective serotonin reuptake inhibitor
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TAG	triacylglyceride
TB	tuberculosis
TCF7L2	transcription factor 7 like 2
TE	transient elastography
TIND	treatment-induced neuropathy in diabetes
TLR	toll-like receptor
TNDM	transient neonatal diabetes mellitus
TNFα	tumor necrosis factor alpha
Treg	regulatory T cell
TSH	thyroid-stimulating hormone
TZD	thiazolidinedione
UKPDS	UK Prospective Diabetes Study
US	ultrasound
UT	University of Texas
VEGF	vascular endothelial growth factor
VLCD	very low calorie diet
VLDL	very low-density lipoprotein
VRIII	variable-rate intravenous insulin infusion
WGS	whole-genome sequencing
WHO	World Health Organization
XO	xanthine oxidase
YY1	Yin Yang 1

A L G r a w a n y

1 Diabetes in its Historical and Social Context

1 The History of Diabetes Mellitus

Robert B. Tattersall[1] and David R. Matthews[2]
[1] University of Nottingham, Nottingham, UK
[2] University of Oxford, Oxford, UK

Key points

- Polyuric diseases have been described for over 3500 years. The name *diabetes* comes from the Greek word for a syphon; the sweet taste of diabetic urine was recognized at the beginning of the first millennium, but the adjective *mellitus* (honeyed) was added by Rollo only in the late eighteenth century.
- The sugar in diabetic urine was identified as glucose by Chevreul in 1815. In the 1840s, Bernard showed that glucose was normally present in blood, and that it was stored in the liver (as glycogen) for secretion into the bloodstream during fasting.
- In 1889, Minkowski and von Mering reported that pancreatectomy caused severe diabetes in the dog. In 1893, Laguesse suggested that the pancreatic *islets* described by Langerhans in 1869 produced an internal secretion that regulated glucose metabolism.
- Insulin was discovered in 1921 by Banting, Best, Macleod, and Collip in acid-ethanol extracts of pancreas. It was first used for treatment in January 1922.
- Diabetes was subdivided on clinical grounds into *diabète maigre* (lean people) and *diabète gras* (obese people) by Lancereaux in 1880, and during the 1930s by Falta and Himsworth into insulin-sensitive and insulin-insensitive types. These classifications were the forerunners of the aetiological classification into type 1 (insulin-dependent) diabetes and type 2 (non-insulin-dependent) diabetes.
- Insulin resistance and β-cell failure, the fundamental characteristics of type 2 diabetes, have been investigated by many researchers. The *insulin clamp* method devised by Andres and DeFronzo was the first accurate technique for measuring insulin action.
- Maturity-onset diabetes of the young was described as a distinct variant of type 2 diabetes by Tattersall in 1974.
- Lymphocytic infiltration of the islets (insulitis) was described as early as 1901 and highlighted in 1965 by Gepts, who suggested that it might be a marker of autoimmunity. Islet cell antibodies were discovered by Doniach and Bottazzo in 1979.
- The primary sequence of insulin was reported in 1955 by Sanger and the three-dimensional structure by Hodgkin in 1969. Proinsulin was discovered by Steiner in 1967, and the sequence of the human insulin gene by Bell in 1980. Yalow and Berson invented the radioimmunoassay for insulin in 1956. The presence of insulin receptors was deduced in 1971 by Freychet, and the receptor protein was isolated in 1972 by Cuatrecasas.
- The various types of diabetic retinopathy were described in the second half of the nineteenth century, as were the symptoms of neuropathy. Albuminuria was noted as a common abnormality in people with diabetes in the nineteenth century and a unique type of kidney disease was described in 1936 by Kimmelstiel and Wilson. The concept of a specific diabetic angiopathy was developed by Lundbæk in the early 1950s.
- Milestones in insulin pharmacology have included the invention of delayed-action preparations in the 1930s and 1940s, synthetic human insulin in 1979, and in the 1990s novel insulin analogues by recombinant DNA technology.
- The first sulfonylurea carbutamide was introduced in 1955, followed by tolbutamide in 1957 and chlorpropamide in 1960. The biguanide phenformin became available in 1959 and metformin in 1960.
- That improved glucose management in both type 1 diabetes and type 2 diabetes was beneficial was proved by the Diabetes Control and Complications Trial (DCCT) in 1993 and the UK Prospective Diabetes Study (UKPDS) in 1998.
- Landmarks in the treatment of complications include photocoagulation for retinopathy, first described by Meyer-Schwickerath; the importance of blood pressure management to slow the progression of nephropathy, demonstrated by Mogensen and Parving; the introduction of low-dose insulin in the treatment of diabetic ketoacidosis in the 1970s; improvements in the care of pregnant women with diabetes pioneered by White and Pedersen; and the emergence of heart failure as a common and treatable pathology.
- The understanding of the complex physiology of type 2 diabetes improved at the beginning of the twenty-first century with clarification of the roles of fat metabolism and signalling; the gut as an endocrine organ; the signals of satiety to the brain; and the role of glucagon as an important homeostatic signal.
- The many therapeutic breakthroughs of the twenty-first century include the discovery of peroxisome proliferator-activated receptor γ (PPAR-γ) activation as a therapy for insulin resistance; the activation of the incretin axis by glucagon-like peptide 1 (GLP-1) receptor agonists and the dipeptidyl peptidase 4 (DPP-4) inhibitors; and the blocking of the renal glucose transporter channels by sodium-glucose cotransporter 2 (SGLT-2) inhibitors.

Professor Robert Tattersall died on 23 November 2020. This historical text is largely his work. Professor David R. Matthews has updated and revised the chapter.

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Ancient times

Diseases with the cardinal features of diabetes mellitus were recognized in antiquity (Table 1.1). A polyuric state was described in an Egyptian papyrus dating from c. 1550 BCE, discovered by Georg Ebers (Figure 1.1), and a clearly recognizable description of what would now be called type 1 diabetes was given by Aretaeus of Cappadocia in the second century CE (Figure 1.2a). Aretaeus was the first to use the term *diabetes*, from the Greek word for a syphon, 'because the fluid does not remain in the body, but uses the man's body as a channel whereby to leave it'. His graphic account of the disease highlighted the incessant flow of urine, unquenchable thirst, the 'melting down of the flesh and limbs into urine', and short survival.

The Hindu physicians Charak and Sushrut, who wrote between 400 and 500 BCE, were probably the first to recognize the sweetness of diabetic urine (Figure 1.2b). Indeed, the diagnosis was made by tasting the urine or seeing that ants congregated round it. Charak and Sushrut noted that the disease was most prevalent in those who were indolent, overweight, and gluttonous, and who indulged in sweet and fatty foods. Physical exercise and liberal quantities of vegetables were the mainstays of treatment in people with obesity, while lean people, in whom the disease was regarded as more serious, were given a nourishing diet. The crucial fact that diabetic urine tasted sweet was also emphasized by Arabic medical texts from the ninth to eleventh centuries CE, notably in the medical encyclopaedia written by Avicenna (980–1037).

Table 1.1 Milestones in the clinical descriptions of diabetes and its complications.

Clinical features of diabetes	
Ebers papyrus (Egypt, 1500 BCE)	Polyuric state
Sushrut and Charak (India, fifth century BCE)	Sugary urine; thin individuals and those with obesity distinguished
Aretaeus (Cappadocia, second century CE)	Polyuric state named *diabetes*
Chen Chuan (China, seventh century CE)	Sugary urine
Avicenna (Arabia, tenth century CE)	Sugary urine; gangrene and impotence as complications
Diabetic ketoacidosis	
William Prout (England, 1810–1820)	Diabetic coma
Adolf Kussmaul (Germany, 1874)	Acidotic breathing
Hyperlipidaemia	
Albert Heyl (Philadelphia, 1880)	Lipaemia retinalis
Retinopathy	
Eduard von Jaeger (Germany, 1855)	General features
Stephen Mackenzie and Edward Nettleship (England, 1879)	Microaneurysms
Edward Nettleship (England, 1888)	New vessels, beading of retinal veins
Julius Hirschberg (Germany, 1890)	Classification of lesions; specific to diabetes
Neuropathy and foot disease	
John Rollo (England, 1797)	Neuropathic symptoms
Marchal de Calvi (France, 1864)	Neuropathy is a complication of diabetes
William Ogle (England, 1866)	Ocular nerve palsies in diabetes
Frederick Pavy (England, 1885)	Peripheral neuropathy
Julius Althaus (Germany, 1890)	Mononeuropathy
Thomas Davies Pryce (England, 1887)	Perforating foot ulcers
Nephropathy	
Wilhelm Griesinger (Germany, 1859)	Renal disease in people with diabetes
Paul Kimmelstiel and Clifford Wilson (USA, 1936)	Glomerulosclerosis associated with heavy proteinuria

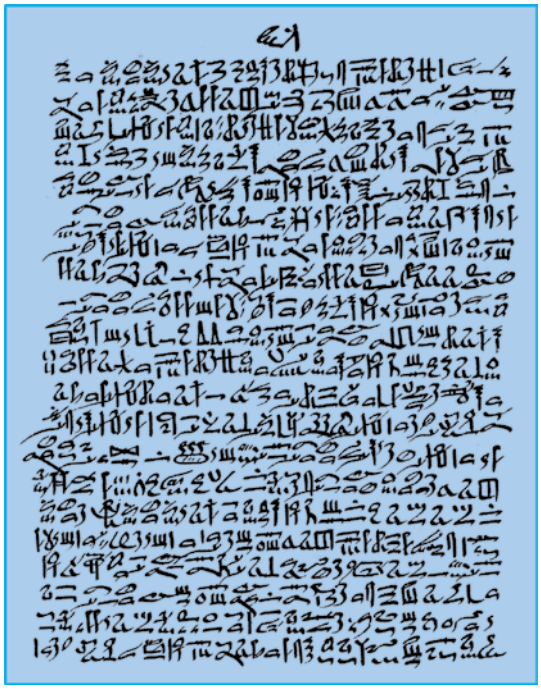


Figure 1.1 The Ebers papyrus. Source: Courtesy of the Wellcome Library, London.

Seventeenth and eighteenth centuries

In Europe, diabetes was neglected until Thomas Willis (1621–1675) wrote *Diabetes, or the Pissing Evil* [1]. According to him, 'diabetes was a disease so rare among the ancients that many famous physicians made no mention of it . . . but in our age, given to good fellowship and guzzling down of unallayed wine, we meet with examples and instances enough, I may say daily, of this disease'. He described the urine as being 'wonderfully sweet like sugar or honey', but did not consider that this might be because it contained sugar.

The first description of hyperglycaemia was in a paper published in 1776 by Matthew Dobson (1735–1784) of Liverpool (Figure 1.3 and Table 1.2) [2]. He found that the serum as well as the urine of his patient Peter Dickonson (who passed 28 pints of urine a day) tasted sweet. Moreover, he evaporated the urine to 'a white cake [which] smelled sweet like brown sugar, neither could it by the taste be distinguished from sugar'. Dobson concluded that the kidneys excreted sugar and that it was not 'formed in the secretory organ but previously existed in the serum of the blood'.

The Edinburgh-trained surgeon, John Rollo (*d.* 1809) was the first to apply the adjective *mellitus* (from the Latin word meaning *honey*). He also achieved fame with his *animal diet*, which became the standard treatment for most of the nineteenth century.

(a)

Diabetes is a dreadful affliction, not very frequent among men, being a melting down of the flesh and limbs into urine. The patients never stop making water and the flow is incessant, like the opening of aqueducts. Life is short, unpleasant and painful, thirst unquenchable, drinking excessive, and disproportionate to the large quantity of urine, for yet more urine is passed. One cannot stop them either from drinking or making water. If for a while they abstain from drinking, their mouths become parched and their bodies dry; the viscera seem scorched up, the patients are affected by nausea, restlessness and a burning thirst, and within a short time, they expire.

(b)

Figure 1.2 (a) Clinical description of diabetes by Aretaeus of Cappadocia (second century CE). Source: Adapted from Papaspyros, N.S. (1952) *The History of Diabetes Mellitus*. (b) Sushrut (Susrata), an Indian physician who wrote medical texts with Charak (Charuka) between 500 BCE and 400 BCE.

MEDICAL

OBSERVATIONS

AND

INQUIRIES.

BY

A SOCIETY OF PHYSICIANS IN LONDON.

VOLUME V.

LONDON:
Printed for T. CADELL, in the Strand.
MDCCLXXVI.

298 *Medical Observations and Inquiries.*

XXVII. *Experiments and Observations on the Urine in a* Diabetes, *by* Matthew Dobſon, *M. D. of* Liverpool; *communicated by Dr.* Fothergill.

SOME authors, eſpecially the Engliſh, have remarked, that the urine in the diabetes is ſweet. Others, on the contrary, deny the exiſtence of this quality, and conſequently exclude it from being a characteriſtic of the diſeaſe. So far as my own experience has extended, and I have met with nine perſons who were afflicted with the diabetes, the urine has always been ſweet in a greater or leſs degree, and particularly ſo in the caſe of the following patient.

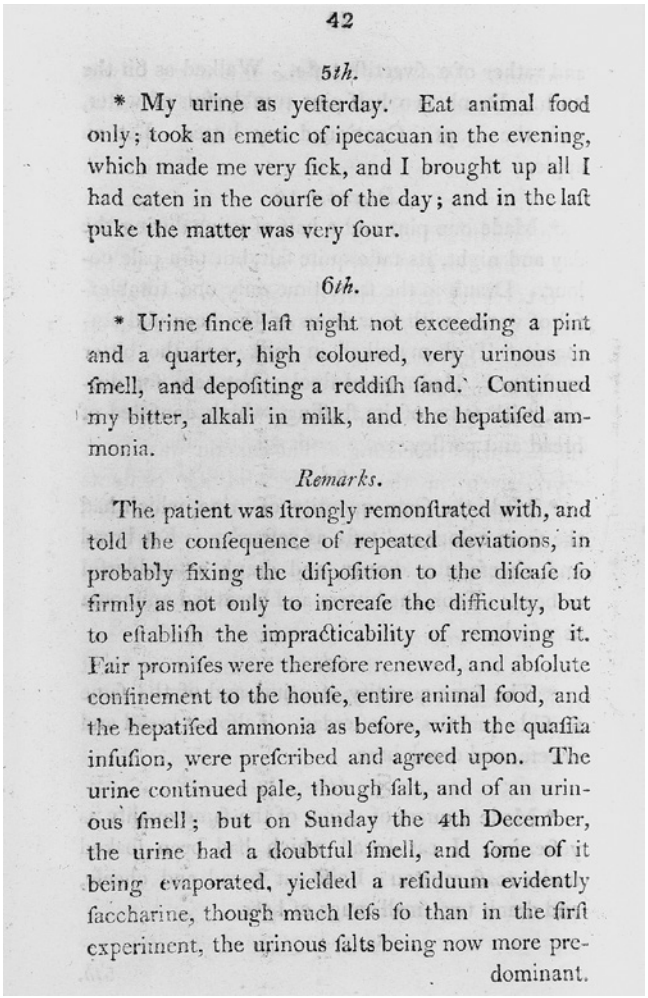
Peter Dickonſon, thirty-three years of age, was admitted into the public hoſpital in Liverpool, October 22, 1772. His diſeaſe was a confirmed diabetes; and he paſſed twenty-eight pints of urine every 24 hours. He had formerly enjoyed a good ſtate of health; nor did it appear what had been the remote cauſes of this indiſpo-

Figure 1.3 Frontispiece and opening page of the paper by Matthew Dobson (1776) in which he described the sweet taste of both urine and serum from a person with diabetes [2].

A L G r a w a n y

Table 1.2 Milestones in the scientific understanding of diabetes and its complications.

Matthew Dobson (England, 1776)	Diabetic serum contains sugar
Michel Chevreul (France, 1815)	The sugar in diabetic urine is glucose
Claude Bernard (France, 1850s)	Glucose stored in liver glycogen and secreted during fasting
Wilhelm Petters (Germany, 1857)	Diabetic urine contains acetone
Paul Langerhans (Germany, 1869)	Pancreatic islets described
Adolf Kussmaul (Germany, 1874)	Describes ketoacidosis
Oskar Minkowski and Josef von Mering (Germany, 1889)	Pancreatectomy causes diabetes in the dog
Gustave Edouard Laguesse (France, 1893)	Glucose-lowering pancreatic secretion produced by islets
M.A. Lane (USA, 1907)	Distinguished A and B islet cells
Jean de Meyer (Belgium, 1909)	Hypothetical islet secretion named *insuline*
Frederick Banting, Charles Best, J.J.R. Macleod, James Collip (Canada, 1922)	Isolation of insulin
Richard Murlin (USA, 1923)	Discovered and named glucagon
Bernado Houssay (Argentina, 1924)	Hypophysectomy enhances insulin sensitivity
Frederick Sanger (England, 1955)	Determined primary sequence of insulin
W.W. Bromer (USA, 1956)	Determined primary sequence of glucagon
Rosalyn Yalow and Solomon Berson (USA, 1959)	Invented radioimmunoassay for insulin
Donald Steiner (USA, 1967)	Discovered proinsulin
Dorothy Hodgkin (England, 1969)	Determined three-dimensional structure of insulin
Pierre Freychet (USA, 1971)	Characterized insulin receptors
Pedro Cuatrecasas (USA, 1972)	Isolated insulin receptor protein
Axel Ullrich (USA, 1977)	Reported sequence of rat insulin
Ralph DeFronzo and Reuben Andres (USA, 1979)	Invented insulin clamp technique
Graham Bell (USA, 1980)	Reported sequence of human insulin gene
Joel Habener (USA), Jens Juel Holst (Denmark) (1986)	Determined primary sequence of glucagon-like peptide 1 (GLP-1)



42

5th.

* My urine as yeſterday. Eat animal food only; took an emetic of ipecacuan in the evening, which made me very ſick, and I brought up all I had caten in the courſe of the day; and in the laſt puke the matter was very ſour.

6th.

* Urine ſince laſt night not exceeding a pint and a quarter, high coloured, very urinous in ſmell, and depoſiting a reddiſh ſand. Continued my bitter, alkali in milk, and the hepatiſed ammonia.

Remarks.

The patient was ſtrongly remonſtrated with, and told the conſequence of repeated deviations, in probably fixing the diſpoſition to the diſeaſe ſo firmly as not only to increaſe the difficulty, but to eſtabliſh the impracticability of removing it. Fair promiſes were therefore renewed, and abſolute confinement to the houſe, entire animal food, and the hepatiſed ammonia as before, with the quaſſia infuſion, were preſcribed and agreed upon. The urine continued pale, though ſalt, and of an urinous ſmell; but on Sunday the 4th December, the urine had a doubtful ſmell, and ſome of it being evaporated, yielded a reſiduum evidently ſaccharine, though much leſs ſo than in the firſt experiment, the urinous ſalts being now more predominant.

Figure 1.4 Extract from John Rollo's account of two cases of diabetes (1797). Rollo was well aware of the problem of not following a treatment regimen. Note that 'the patient was strongly remonstrated with, and told of the consequences of repeated deviations'. Source: Courtesy of the Wellcome Library, London.

Rollo thought that sugar was formed in the stomach from vegetables and concluded that the obvious solution was a diet of animal food. Thus, the regimen described in his 1797 book, *An Account of Two Cases of the Diabetes Mellitus* [3], allowed his patient Captain Meredith to have for dinner 'Game or old meats which have been long kept; and as far as the stomach may bear, fat and rancid old meats, as pork'. Rollo was probably the first to note the difficulty that some people with diabetes find in following a treatment regimen, a difficulty he blamed for the death of his second patient (Figure 1.4).

Nineteenth century

In 1815, the French chemist Michel Chevreul (1786–1889) proved that the sugar in diabetic urine was glucose [4]. In the middle of the century, tasting the urine to make the diagnosis was superseded by chemical tests for reducing agents such as glucose, as introduced by Trommer in 1841, Moore in 1844, and – the best known – Fehling in 1848. Measurement of blood glucose could only be done by skilled chemists, but needed so much blood that it was rarely used in either clinical care or research. It only became practicable with the introduction in 1913 of a micromethod by the Norwegian-born physician Ivar Christian Bang (1869–1918), and it was the ability to measure glucose repeatedly that led to development of the glucose tolerance test between 1913 and 1915.

Glucose metabolism was clarified by the work of Claude Bernard (1813–1878) [5], the Frenchman whose numerous discoveries have given him a special place in the history of physiology (Figure 1.5). When Bernard began work in 1843, the prevailing theory was that sugar could only be synthesized by plants, and that animal metabolism broke down substances originally made in plants. It was also thought that the blood only contained sugar after meals, or in pathological states such as diabetes. Between 1846 and 1848, Bernard reported that glucose was present in the blood of normal animals, even when starved. He also found higher concentrations of glucose in the hepatic than in the portal vein, and 'enormous quantities' of a starch-like substance in the liver that could be readily converted into sugar. He called this *glycogen* (i.e. sugar-forming) and regarded it as analogous to starch in plants. His hypothesis – the *glycogenic* theory – was that sugar absorbed from the intestine was

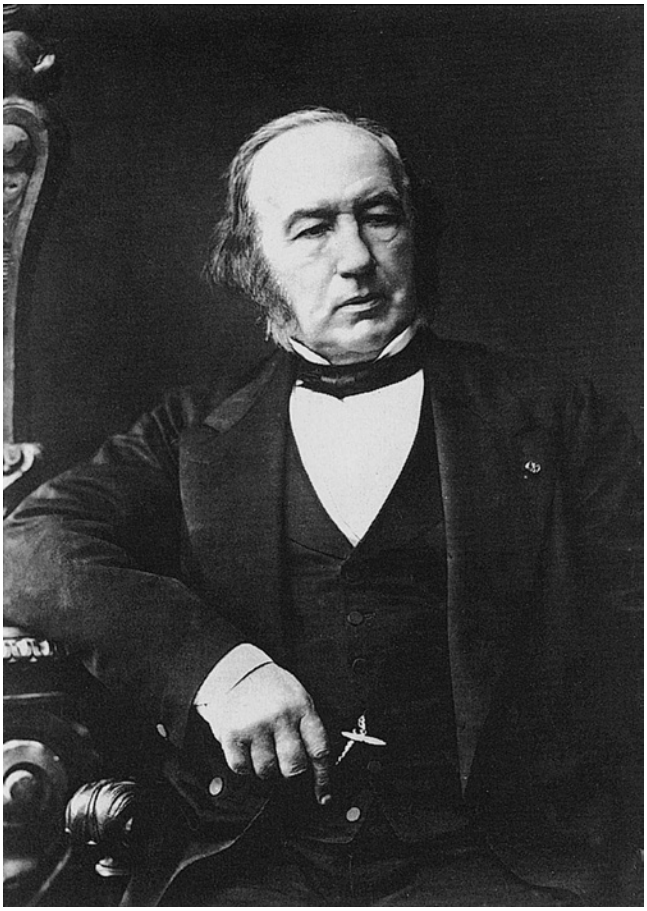


Figure 1.5 Claude Bernard (1813–1878). Source: Courtesy of the Wellcome Library, London.

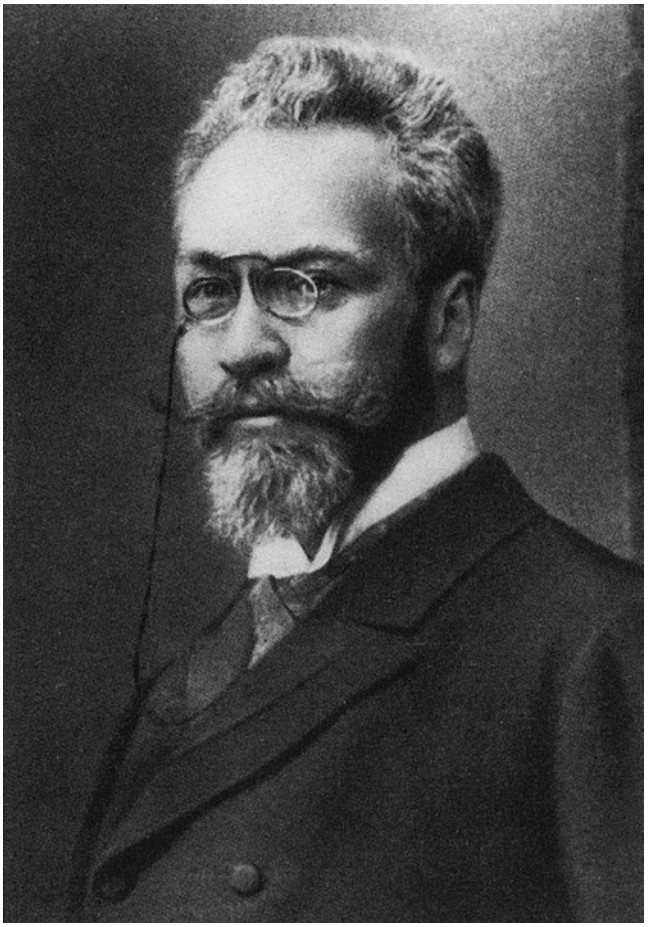


Figure 1.6 Oskar Minkowski (1858–1931).

converted in the liver into glycogen and then constantly released into the blood during fasting.

Another discovery by Bernard made a great impression in an era when the nervous control of bodily functions was a scientifically fashionable concept. He found that a lesion in the floor of the fourth ventricle produced temporary hyperglycaemia (*piqûre* diabetes) [6]. This finding spawned a long period in which nervous influences were thought to be important causes of diabetes; indeed, one piece of 'evidence' – cited by J.J.R. Macleod as late as 1914 – was that diabetes was more common among engine drivers than other railway workers because of the mental strain involved [7].

In the first part of the nineteenth century the cause of diabetes was a mystery, because autopsy usually did not show any specific lesions. A breakthrough came in 1889 when Oskar Minkowski (Figure 1.6) and Josef von Mering (1849–1908) reported that pancreatectomy in the dog caused severe diabetes [8]. This was serendipitous, because they were investigating fat metabolism; it is said that the laboratory technician mentioned to Minkowski that the dog, previously house-trained, was now incontinent of urine. Minkowski realized the significance of the polyuria, and tested the dog's urine (Table 1.3).

Possible explanations for the role of the pancreas were that it removed a diabetogenic toxin, or produced an internal secretion that regulated carbohydrate metabolism. The concept of *internal*

Table 1.3 Milestones in the understanding of the causes of diabetes.

Thomas Willis (England, seventeenth century)	Overindulgence in food and drink
Thomas Cawley (England, 1788)	Pancreatic stones cause diabetes
Oskar Minkowski and Josef von Mering (Germany, 1889)	Pancreatectomy causes diabetes in the dog
Etienne Lancereaux (France, 1880)	Lean and obese subtypes of diabetes distinguished
Eugene Opie (USA, 1900)	Hyaline degeneration (amyloidosis) of islets (type 2 diabetes)
Eugene Opie (USA, 1910)	Lymphocytic infiltration of islets (*insulitis*; type 1 diabetes)
Wilhelm Falta (Vienna) and Harold Himsworth (England, early 1930s)	Distinguished insulin-resistant and insulin-sensitive forms of diabetes
Willy Gepts (Belgium, 1965)	Suggested that insulitis caused β-cell destruction (type 1 diabetes)
Deborah Doniach and GianFranco Bottazzo (England, 1979)	Suggested that insulin-dependent diabetes is an autoimmune disease
Andrew Cudworth and John Woodrow (England, 1975)	Insulin-dependent diabetes associated with specific human leucocyte antigens

Figure 1.7 Paul Langerhans (1847–1888). Source: Courtesy of the Wellcome Library, London.

secretions had been publicized in June 1889 by the well-known physiologist Charles-Édouard Brown-Séquard (1817–1894), who claimed to have rejuvenated himself by injections of testicular extract [9]. It was given further credence in 1891, when Murray reported that myxoedema could be cured by sheep thyroid extract by injection or orally.

In 1893, Gustave Laguesse suggested that the putative internal secretion of the pancreas was produced by the *islands* of cells scattered through the gland's parenchyma [10], which had been discovered in 1869 by the 22-year-old Paul Langerhans (1847–1888) (Figure 1.7). Langerhans had described these clusters of cells, having teased them out from the general pancreatic tissue, but had not speculated about their possible function [11]; it was Laguesse who named them the *islets of Langerhans*. At this time the glucose-lowering internal secretion of the islets was still hypothetical, but in 1909 the Belgian Jean de Meyer named it *insuline* (from the Latin for *island*) [12].

It would be wrong to give the impression that Minkowski's experiments immediately established the pancreatic origin of diabetes. In fact, during the next two decades it was widely agreed that diabetes was a heterogeneous disorder with various subtypes, and that its pathogenesis involved at least three organs: brain, pancreas, and liver [13]. The discovery by Blum in 1901 that injection of an adrenal extract caused glycosuria implicated other glands, and led to the *polyglandular theory* of Carl von Noorden (Vienna), who proposed that the thyroid, pancreas, adrenals, and parathyroids controlled carbohydrate metabolism.

Clinical diabetes in the nineteenth century

Doctors in the nineteenth century were therapeutically impotent; their main role was as taxonomists who described symptom complexes and the natural history of disease. As a result, most of the major complications of diabetes were well described before 1900. Eduard von Jaeger (1818–1884) is credited with the first description of diabetic retinopathy, in his beautiful *Atlas of Diseases of the Ocular Fundus*, published in 1869 [14]. In fact, the features illustrated (Figure 1.8), from a 22-year-old man, look more like hypertensive retinopathy. In 1879, Stephen Mackenzie (1844–1909) and Sir Edward Nettleship (1845–1913) found microaneurysms in flat preparations of the retina and, in 1888, Nettleship described new vessels and the beaded appearance of retinal veins [15]. The full picture of diabetic retinopathy was described in 1890 by Julius Hirschberg (1843–1925), who was the first to claim that it was specific to diabetes [16].

Neuropathic symptoms in people with diabetes had been mentioned by Rollo at the end of the eighteenth century, and in 1864 Charles Marchal de Calvi (1815–1873) concluded that nerve damage was a specific complication of diabetes. In 1885, the Guy's Hospital physician Frederick Pavy (1829–1911) gave a description of neuropathic symptoms that could grace any modern textbook [17]:

> *The usual account given by these patients of their condition is that they cannot feel properly in their legs, that their feet are numb, that their legs seem too heavy – as one patient expressed it, 'as if he had 20 lb weights on his legs and a feeling as if his boots were great deal too large for his feet.' Darting or 'lightning' pains are often complained of. Or there may be hyperaesthesia, so that a mere pinching of the skin gives rise to great pain; or it may be the patient is unable to bear the contact of the seam of the dress against the skin on account of the suffering it causes. Not infrequently there is deep-seated pain located, as the patient describes it, in the marrow of the bones which are tender on being grasped, and I have noticed that these pains are generally worse at night.*

Pavy also recorded unusual presentations, including a 67-year-old who complained of 'lightning pains on the right side of the waist' and cases in which the third nerve was affected with 'dropped lid and external squint' [18].

Kidney disease was known to be relatively common in diabetes. In 1859, Wilhelm Griesinger (1817–1868) reported 64 autopsies in adults, half of whom had renal changes that he attributed to hypertension and atherosclerosis [19]; however, the histological features of diabetic kidney disease and the importance of renal complications were not reported until the 1930s.

In the latter part of the nineteenth century it was becoming apparent that there were at least two clinically distinct forms of diabetes. In 1880, the French physician Etienne Lancereaux (1829–1910) identified individuals who were lean and those with obesity as having *diabète maigre* and *diabète gras*, respectively [20], and this observation laid the foundations for subsequent aetiological classifications of the disease.

Twentieth century

Murray's cure of myxoedema in 1891 led to a belief that pancreatic extract would soon result in a cure for diabetes, but, in the face of repeated failures over the next 30 years, even believers in an anti-diabetes internal secretion were depressed about the likelihood of isolating it, and diverted their attention to diet as a treatment for the disease.

Best known was the starvation regimen of Frederick Madison Allen (1876–1964), which Joslin (Figure 1.9) described in 1915 as the greatest advance since Rollo's time [22]. This approach was an

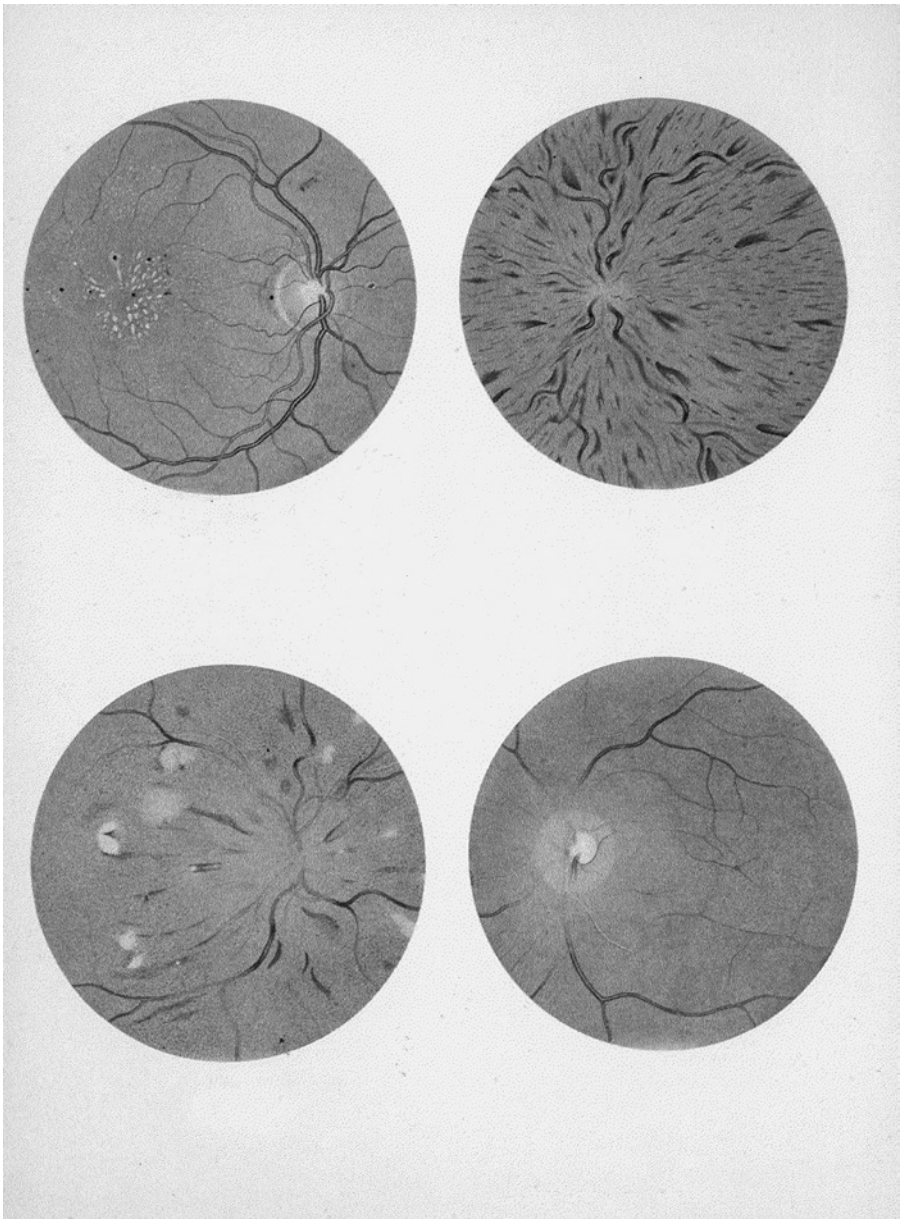


Figure 1.8 Pictures from *Jaeger's Atlas of the Optic Fundus*, 1869 [14]. Top left: Bright's disease. Top right: Jaeger's retinitis haemorrhagica is now recognized as central retinal vein occlusion. Bottom left: A 22-year-old man with suspected diabetes. Bottom right: Central retinal artery occlusion. Source: Courtesy of W.B. Saunders.

extreme application of one that had been proposed as early as 1875 by Apollinaire Bouchardat (1806–1886), who advocated intensive exercise and '*manger le moins possible*'. Starvation treatment did work in a limited sense, in that some people could survive for many months or even years, instead of a few weeks or months with untreated type 1 diabetes. The quality of life, however, was very poor, and some died of malnutrition rather than diabetes. In 1921, Carl von Noorden (1858–1944), proponent of the *oatmeal cure,* turned away in disapproval when he saw Joslin's prize patient, 17-year-old Ruth A, who at just over 1.52 m in height weighed only 24.5 kg (a body mass index of 10.6 kg/m^2).

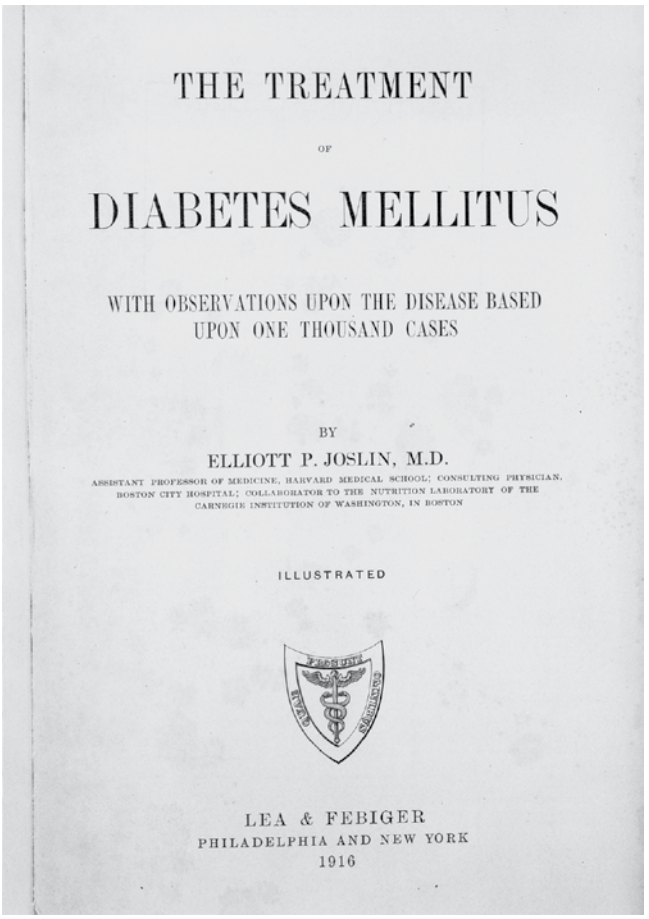
Discovery of insulin

Many attempts were made between 1889 and 1921 to isolate the elusive internal secretion of the pancreas. These largely failed because the extracts were inactive or had unacceptable side effects; some preparations may have had limited biological activity, but this was not recognized, either because hypoglycaemia was misinterpreted as a toxic reaction or because blood glucose was not measured. Those who came closest were the Berlin physician Georg Zuelzer (1840–1949) in 1907 [23], Ernest Scott (1877–1966) in Chicago in 1911 [24], and Nicolas Paulesco (1869–1931) in Romania in 1920–1921 [25] (Figure 1.10).

The story of how insulin was discovered in Toronto in 1921 is well known, at least superficially (Figure 1.11). A young orthopaedic surgeon, Frederick Banting, inspired after reading an article by the pathologist Moses Barron (1884–1975), wondered whether the anti-diabetes pancreatic principle was digested by trypsin during extraction, and decided to prevent this loss by ligating the pancreatic duct, thus causing the exocrine tissue to degenerate. He approached the professor of physiology in Toronto, J.J.R. Macleod, an authority on carbohydrate metabolism, who poured scorn on the idea and suggested that the only likely outcome would be 'a negative result of great physiological importance'.

(a)

(b)



THE TREATMENT

OF

DIABETES MELLITUS

WITH OBSERVATIONS UPON THE DISEASE BASED UPON ONE THOUSAND CASES

BY

ELLIOTT P. JOSLIN, M.D.

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL; CONSULTING PHYSICIAN, BOSTON CITY HOSPITAL; COLLABORATOR TO THE NUTRITION LABORATORY OF THE CARNEGIE INSTITUTION OF WASHINGTON, IN BOSTON

ILLUSTRATED

LEA & FEBIGER

PHILADELPHIA AND NEW YORK

1916

Figure 1.9 (a) Elliott P. Joslin (1869–1962), arguably the most famous diabetes specialist of the twentieth century, and (b) the frontispiece to his 1916 textbook [21]. Source: Courtesy of the Wellcome Library, London.

Eventually, Macleod relented and installed Banting in a rundown laboratory, later leaving for Scotland and a fishing holiday. A student, Charles Best, was chosen by the toss of a coin to help Banting. Within six months of this unpromising start, Banting and Best (referred to in Toronto academic circles as B^2) had discovered the most important new therapy since the anti-syphilitic agent salvarsan. These events are described in detail in the excellent book by Michael Bliss [26].

Their approach began with the injection of extracts of atrophied pancreas (prepared according to Macleod's suggestions) into dogs rendered diabetic by pancreatectomy. Subsequently, they discovered that active extracts could be obtained from beef pancreas, which Best obtained from the abattoir. The extraction procedure (using ice-cold acid-ethanol) was greatly refined by James B. (Bert) Collip, a biochemist who was visiting Toronto on sabbatical leave.

The first clinical trial of insulin (using an extract made by Best) took place on 11 January 1922, on 14-year-old Leonard Thompson, who had been on the Allen starvation regimen since 1919 and weighed only 30 kg (Figure 1.12). After the first injection, his blood glucose level fell slightly, but his symptoms were unchanged and he developed a sterile abscess. On 23 January, he was given another extract prepared by Collip, and this normalized his blood glucose by the next morning; further injections over the next 10 days led to marked clinical improvement and complete elimination of glycosuria and ketonuria. Initial clinical results in seven cases were published in the March 1922 issue of the *Canadian Medical Association Journal* [27], which had the following dramatic conclusions:

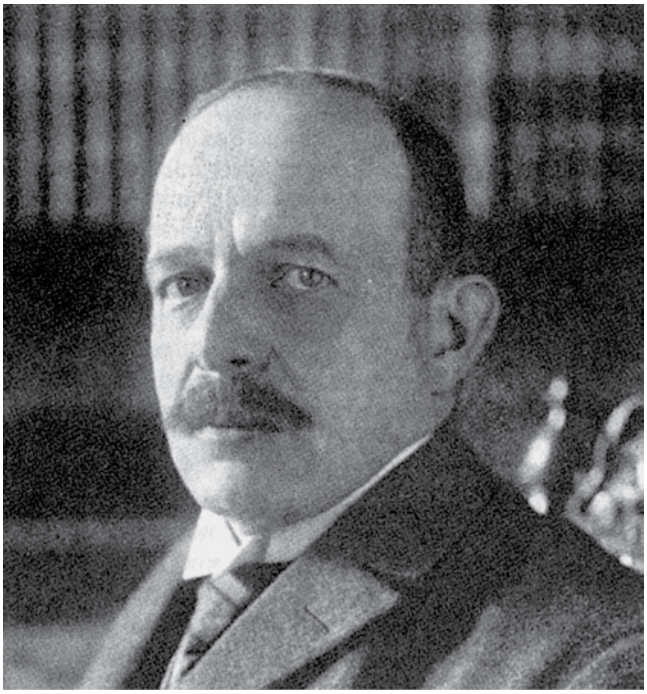
- Blood sugar can be markedly reduced, even to normal values.
- Glycosuria can be abolished.
- The acetone bodies can be made to disappear from the urine.
- The respiratory quotient shows evidence of increased utilization of carbohydrates.
- A definite improvement is observed in the general condition of these patients and, in addition, the patients themselves report a subjective sense of well-being and increased vigour for a period following the administration of these preparations.

The term *insulin* was coined by Macleod, who was unaware of de Meyer's earlier suggestion of *insuline*. News of its miraculous effects spread astonishingly rapidly [28]. In 1922, there were only 19 references in the world literature to *insulin* or equivalent terms such as *pancreatic extract*; by the end of 1923, there were 320 new reports, and a further 317 were published during the first six months of 1924.

By October 1923, insulin was available widely throughout North America and Europe. International recognition followed rapidly for its discoverers, and the 1923 Nobel Prize for Physiology or Medicine was awarded jointly to Banting and Macleod. Banting

A L G r a w a n y

(a)



(b)

Experimentelle Untersuchungen über den Diabetes.[1])

Kurze Mitteilung.[2])

Von

G. Zuelzer.

F. Blum hat vor einigen Jahren gezeigt, dass subkutane oder intravenöse Injektion von Nebennierensaft bei den verschiedensten Tieren Glykosurie hervorruft, die 48 bis 74 Stunden anhalten kann. Ich, und kurze Zeit darauf Metzger wiesen nach, dass gleichzeitig eine Hyperglykämie besteht, dass es sich beim Nebennierendiabetes also nicht etwa um ein Analogon des Phloridzindiabetes, um einen sogenannten Nierendiabetes handeln könne. Während ich mich dahin aussprach, dass dieser Diabetes seiner ganzen Natur nach dem richtigen Diabetes ähnele, nur durch die Dauer seines Bestehens von ihm unterschieden sei und naturgemäss auch keine Tendenz zum Fortschreiten zeigen, i. e. niemals das Endstadium des gewöhnlichen schweren menschlichen Diabetes darbieten könne, wurde die in Frage stehende Glykosurie von den meisten anderen Autoren als eine ziemlich belanglose toxische Glykosurie aufgefasst.

Es schien mir nicht sehr wahrscheinlich, dass ein Körper, der anscheinend unverändert, wie er normalerweise produziert und dauernd[3]) dem Säftestrom des Organismus zugeführt wird, dass ein solcher, quasi physiologischer Körper eine vollkommen unphysiologische Wirkung sollte hervorbringen können. Ich habe also versucht, den Ort des Angriffs des Nebennierensaftes[4]), sowie die Ursachen seiner toxischen Wirkung näher zu erforschen. Ich folgte dabei, wie gesagt, stets dem Gedanken, in dem Nebennierendiabetes ein, wenn auch nur flüchtiges Bild gewisser menschlicher Diabetesformen zu finden.

So untersuchte ich zuerst, welchen Einfluss hat der Nebennierensaft auf die Leber als dasjenige Organ, welches, allgemein ausgedrückt, mit der Zuckerregulierung im Körper in erster

1) Die Untersuchungen wurden zum Teil mit Unterstützung der Gräfin Bose-Stiftung im physiologischen Institut der Berliner Universität, und zwar noch unter Mithilfe der verstorbenen Proff. I. Munk und Paul Schultz ausgeführt.

2) Diese kurze Mitteilung wurde der Redaktion bereits vor ca. 3 Jahren eingereicht. Die Drucklegung unterblieb auf Wunsch des Verf. in der bisher nicht erfüllten Erwartung, dass es gelingen würde, aus den theoretischen Untersuchungen praktisch-therapeutische Resultate zu erzielen.

3) Durch Versuche von Ehrmann, Archiv f. experim. Pathol. u. Pharmakol., Bd. 55, ist inzwischen der Nachweis erbracht worden, dass die Adrenalinsekretion konstant vor sich geht.

4) In meinen ersten Versuchen bediente ich mich des von mir selbst hergestellten Nebennierensaftes. In den zahlreichen späteren Versuchen habe ich inzwischen genau die gleichen Wirkungen mit den verschiedenartig hergestellten käuflichen Adrenalinpräparaten feststellen können.

(c)

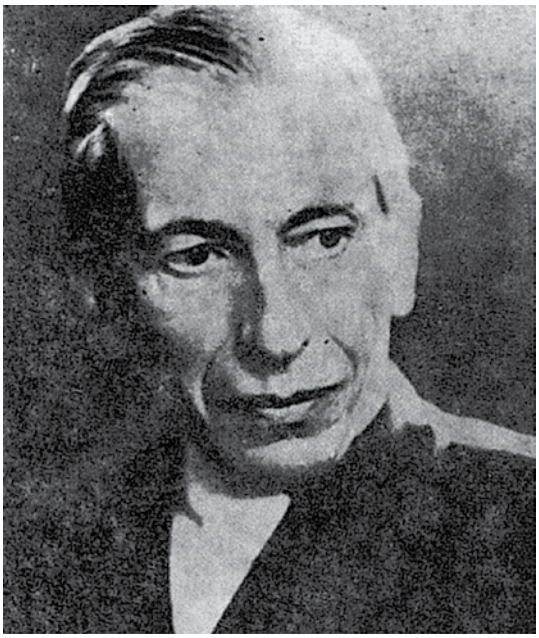


Figure 1.10 (a) Georg Zuelzer (1840–1949) and (b) the title page from his paper (1907) reporting that a pancreatic extract reduced glycosuria in pancreatectomized dogs [23]. (c) Nicolas Paulesco (1869–1931).

was angered by the decision, and announced publicly that he would share his prize with Best, whereupon Macleod decided to do the same with Collip.

The post-insulin era

It was confidently anticipated that insulin would do for diabetes in the young what thyroid extract had done for myxoedema, but it soon became obvious that insulin was a very different type of treatment. Thyroid was given once a day by mouth and at a fixed dosage. Insulin had to be injected in measured amounts that varied from day to day, and carried the ever-present danger of hypoglycaemia. One often reads that insulin 'revolutionized' the treatment of diabetes; it did so in the sense that it saved the lives of many who would otherwise have died, but its unforeseen effect was to transform an acute, rapidly fatal illness into a chronic disease with serious long-term complications. For example, only 2% of deaths among Joslin's young patients with diabetes before 1937 were caused by kidney disease, while over 50% dying between 1944 and

Figure 1.11 The discoverers of insulin. (a) Frederick G. Banting (1891–1941); (b) James B. Collip (1892–1965); (c) J.J.R. Macleod (1876–1935); and (d) Charles H. Best (1899–1978). Source: Courtesy of the Fisher Rare Book Library, University of Toronto.

Figure 1.12 Leonard Thompson, the first person to receive insulin, in January 1922. Source: Courtesy of the Fisher Rare Book Library, University of Toronto.

1950 had advanced renal failure. Strategies to avoid and prevent the chronic complications of diabetes remain important scientific and clinical priorities today.

The rest of this chapter highlights some developments that can be regarded as landmarks in the understanding and management of the disease; to some extent this is a personal choice, and it is obvious from the other chapters in this book that the *history* of diabetes is being rewritten all the time.

Causes and natural history of diabetes

The recognition that diabetes was not a single disease was important in initiating research that has helped to unravel the causes of hyperglycaemia.

The broad aetiological subdivision into type 1 (juvenile-onset, or insulin-dependent) diabetes and type 2 diabetes (maturity-onset, or non-insulin-dependent) stemmed ultimately from Lancereaux's *diabète maigre* and *diabète gras* distinction, as well as observations soon after the discovery of insulin that some individuals did not react *normally* to insulin. In the 1930s, Wilhelm Falta (1875–1950) in Vienna [29] and Harold Himsworth (1905–1993) in London [30] proposed that some individuals with diabetes were more sensitive to the glucose-lowering effects of insulin, whereas others were

insulin insensitive, or insulin resistant. The former were usually thin and required insulin to prevent ketoacidosis, while the latter were older, had obesity, and were ketosis resistant.

The *insulin clamp* technique developed in the 1970s by Ralph DeFronzo and colleagues [31] in the USA was the first to measure rigorously the hypoglycaemic action of insulin, and has led to countless studies of insulin resistance and its relationship to type 2 diabetes and vascular disease. Various groups, including DeFronzo's, have helped to clarify the role of β-cell failure in type 2 diabetes, and how it relates to insulin resistance. Maturity-onset diabetes of the young (MODY) was recognized in 1974 by Robert Tattersall (1943–2020) as a distinct, dominantly inherited subset of type 2 diabetes [32]; since 1993 many different molecular defects have been identified in this condition.

The causes of the profound β-cell loss that led to the severe insulin deficiency of type 1 diabetes remained a mystery for a long time. *Insulitis*, predominantly lymphocytic infiltration of the islets, was noted as early as 1901 by Eugene L. Opie (1873–1971) and colleagues [33], but because it was apparently very rare, found in only 6 of 189 cases studied by Anton Weichselbaum (1845–1920) in 1910, its importance was not appreciated. The possible role of insulitis in β-cell destruction was not suggested until 1965, by the Belgian Willy Gepts (1922–1991) [34]. The theory that type 1 diabetes results from autoimmune destruction of the β cells was first made in 1979 by Deborah Doniach (1912–2004) and GianFranco Bottazzo (1946–2017) [35]. Unlike other autoimmune endocrine diseases where the autoantibody persists, islet cell antibodies turned out to be transient and disappeared within a year of the onset of diabetes. An unexpected finding from the Barts–Windsor prospective study of the epidemiology of diabetes in childhood started by Andrew Cudworth (1939–1982) was that islet cell antibodies could be detected in siblings of young people with diabetes up to 10 years before they developed apparently acute-onset diabetes. This long lead-in period raised the possibility of an intervention to prevent continuing β-cell destruction. Cyclosporine in people with newly diagnosed type 1 diabetes prolonged the honeymoon period, but without permanent benefit once the drug was stopped [36]. Nicotinamide and small doses of insulin (together with many other interventions) prevented diabetes in the non-obese diabetic (NOD) mouse, but were without effect in relatives of people with type 1 diabetes with high titres of islet cell antibodies [37, 38].

From 1967, when Paul Lacy (1924–2005) showed that it was possible to *cure* diabetes in inbred rats with an islet cell transplant, it always seemed that the problem of islet cell transplantation in humans was about to be solved. Hope was rekindled in 2000 by a team in Edmonton, Canada. After five years 80% of those who had received a transplant were producing some endogenous insulin, but only 10% could manage without any injected insulin [39].

Chronic diabetic complications

It had been assumed that arteriosclerosis caused chronic diabetic complications, but this notion was challenged by two papers published in the mid-1930s, which pointed to specific associations of diabetes with retinal and renal disease (Table 1.2). In 1934, Henry Wagener (1890–1961) and Russell Wilder (1885–1959) from the Mayo Clinic reported people who had retinal haemorrhages but no other clinical evidence of vascular disease [40], and concluded that 'The very existence of retinitis in cases in which patients have no other signs of vascular disease must mean that diabetes alone does something to injure the finer arterioles or venules of the retina, probably the latter'.

Figure 1.13 Nodular glomerulosclerosis. Figure from the paper by Kimmelstiel and Wilson, 1936 [41]. Source: Courtesy of the British Medical Association Library.

In 1936, Paul Kimmelstiel (1900–1970) and Clifford Wilson (1906–1997) described the striking histological finding of *intercapillary glomerulosclerosis,* large hyaline nodules in the glomeruli in the kidneys of eight people at autopsy (Figure 1.13) [41]. Seven of the eight individuals had a known history of diabetes, and Kimmelstiel and Wilson noted the common features of hypertension, heavy albuminuria with 'oedema of the nephrotic type', and renal failure. In fact, this paper led to considerable confusion during the next 15 years: according to one writer, the *Kimmelstiel–Wilson syndrome* came to mean all things to all people [42]. Nonetheless, it was significant because it drew attention to a specific diabetic renal disease.

Acceptance of the concept that diabetic angiopathy was specific to the disease owed much to the work of Knud Lundbæk from Aarhus, Denmark (Figure 1.14), who published his findings in a book in 1953–1954 and a paper in the *Lancet* in 1954 [43, 44]. His key arguments were that long-standing diabetic vascular disease differed fundamentally from atherosclerosis, in that both sexes were equally affected, and that microaneurysms, ocular phlebopathy, and Kimmelstiel–Wilson nodules were unique to diabetes and usually occurred together.

The molecular and cellular mechanisms underlying diabetic tissue damage remain controversial after decades of intensive research.

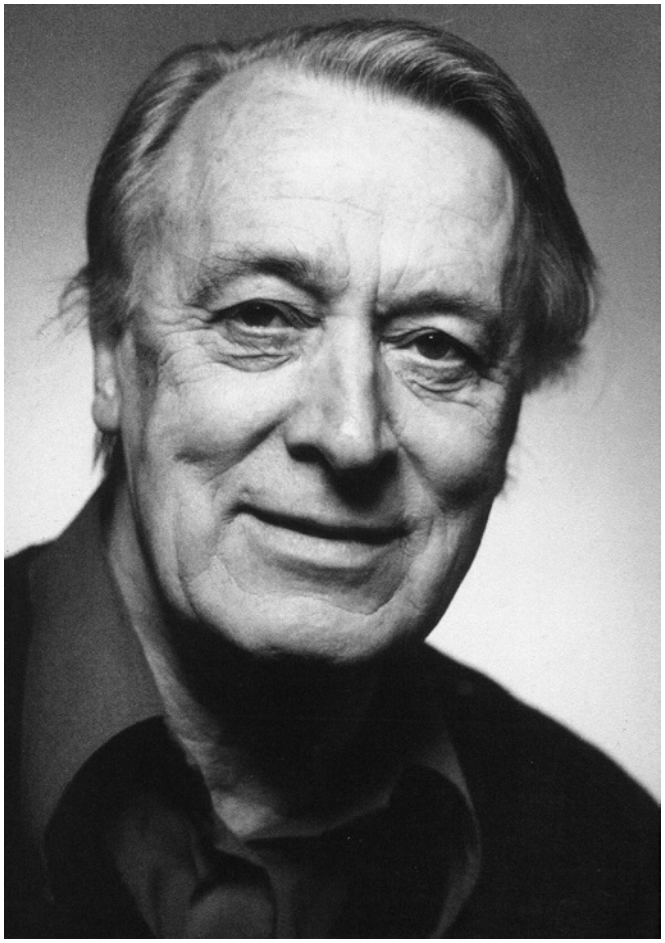


Figure 1.14 Knud Lundbæk (1912–1995). Source: Courtesy of Dr Carl Erik Mogensen.

One of the early landmarks in this field was the work of J.H. Kinoshita (*b.* 1922) during the early 1970s, which pointed to the involvement of the polyol pathway in the formation of diabetic cataracts [45].

Physiology

In 1907, M.A. Lane, a student of Robert Bensley (1867–1956), professor of anatomy in Chicago, used conventional histological techniques to distinguish two different cell types in the islet of Langerhans, which he termed A and B [46]. The hormones secreted by these respective cell types were not identified until much later (Table 1.2). Frank Young (1908–1988) and colleagues reported in 1938 that injections of anterior pituitary extract could induce permanent diabetes in the dog, and that this was accompanied by selective degranulation and loss of the β cells [47]; it was surmised that these cells produced insulin, and this was finally confirmed using immuno-histochemistry by Paul Lacy in 1959 [48]. Glucagon was similarly localized to the α cells in 1962 by John Baum and colleagues [49].

The amino acid sequence of insulin was reported in 1955 by Frederick Sanger in Cambridge, UK [50], and the three-dimensional structure of the molecule in 1969 by Dorothy Hodgkin in Oxford [51]; both discoveries were recognized by the award of Nobel Prizes (Figure 1.15). The complete insulin molecule was synthesized from amino acids by Wang Ying-lai (1908–2001) and colleagues in Shanghai in 1965 [52]. The insulin precursor, proinsulin, was described in 1967 by Donald Steiner (1930–2014) in Chicago [53]. The first bioassay for insulin, based on the hormone's ability to lower blood glucose in the alloxan-diabetic rat, was reported in 1950 by the Australian Joseph Bornstein (1918–1994), working in London with Robin D. Lawrence [54]. This method was superseded in 1956 by Rosalyn Yalow and Solomon Berson in the

(a)

(b)

Figure 1.15 (a) Frederick Sanger (1918–2013) and (b) Dorothy Hodgkin, née Crowfoot (1910–1994). Source: Courtesy of Godfrey Argent Studio, London.

Figure 1.16 Solomon Berson and Rosalyn Yalow.

USA, who discovered that insulin was antigenic; they exploited the binding of the hormone to anti-insulin antibodies to develop the first radioimmunoassay [55]. This assay method revolutionized endocrinology – and, indeed, many areas of physiology and medicine – and was also rewarded with a Nobel Prize (Figure 1.16).

The sequence of rat insulin genes was described in 1977 by Axel Ullrich (*b*. 1945) and colleagues [56], and the human sequence by Graham Bell (*b*. 1948) and his group in 1980 [57]. The existence of insulin receptors was inferred from the insulin-binding characteristics of liver-cell membranes by Pierre Freychet (*b*. 1935) and colleagues in 1971 [58], and the receptor protein was isolated by Pedro Cuatrecasas (*b*. 1936) in the following year [59]. The gene encoding the insulin receptor was cloned and sequenced in 1985 by two groups [60, 61]. In recent years, numerous advances have helped to clarify how insulin exerts its biological actions. Among these was the discovery in 1985 of the first of the glucose transporter (GLUT) proteins by Mueckler and colleagues in the USA [62].

Management of diabetes

An objective observer surveying clinical diabetes during the half-century after the discovery of insulin and the 'resurrection' (a word used by Joslin) of young people with diabetes would have been dismayed by what they saw (Table 1.4). In particular, young people were dying of complications that had previously been assumed to be the preserve of older people. Two particularly depressing papers were published in 1947 and 1950. First, Henry Dolger (1909–1997) in New York described 20 people who fulfilled the then-accepted criteria for excellent *diabetic control*, but who all developed severe retinopathy after 6–22 years [72]; among these was the first person ever to receive insulin at Mount Sinai Hospital, New York, who also had heavy albuminuria and hypertension by the age of 32. Second, Ruth Reuting reported a cohort of 50 young individuals with diabetes originally identified in 1929 [73]. By 1949, one-third had died (mostly from cardiovascular and renal disease) at an average age of 25 years, after only 18 years of diabetes, and the survivors showed 'ominous signs of hypertension, azotemia, and proteinuria in significant numbers'. This had occurred despite the introduction of more versatile insulin preparations; the situation was so hopeless that it inaugurated 20 years of treatment with 'heroic' measures such as adrenalectomy and hypophysectomy.

Table 1.4 Selected milestones in the management of diabetes.

Lifestyle modification	
Li Hsuan (China, seventh century)	Avoid wine, sex, and salty cereals
Thomas Willis (England, seventeenth century)	Food restriction
John Rollo (England, 1797)	Animal diet
Apollinaire Bouchardat (France, 1875)	Food restriction and increased exercise
Carl von Noorden (Germany, 1903)	Oatmeal cure
Frederick Allen (USA, 1913)	Starvation diet for early-onset diabetes
Karl Petrén (Sweden, 1915)	High-fat, low-carbohydrate diet
Roy Taylor (England, 2015) [63]	Very low-calorie diet – remission of diabetes
Insulin treatment	
Georg Zuelzer (Germany, 1907) and Nicolas Paulesco (Romania, 1921)	Isolated pancreatic extracts with hypoglycaemic activity
Frederick Banting, Charles Best, J.J.R. Macleod, and James Collip (Canada, 1922–1923)	Isolation and first clinical use of insulin
Hans Christian Hagedorn (Denmark, 1936)	Protamine insulin, the first long-acting insulin
David Goeddel (USA, 1979)	Synthetic human-sequence insulin produced by recombinant DNA technology
John Pickup (London, 1978)	Described continuous subcutaneous insulin infusion
John Ireland (Scotland, 1981)	Invented pen-injection device
Oral anti-diabetes agents	
Avicenna (Arabia, tenth century)	Recommended lupin, fenugreek, and zedoary seeds
Willhelm Ebstein (Germany, 1876)	Recommended sodium salicylate
E. Frank (Germany, 1926)	Biguanide derivative (Synthalin) introduced, but withdrawn because of toxicity
Celestino Ruiz (Argentina, 1930)	Noted hypoglycaemic action of some sulfonamides
Auguste Loubatières (France, 1942)	Discovered hypoglycaemic action of prototype sulfonylurea
H. Franke and J. Fuchs (Germany, 1955)	Carbutamide introduced
G. Ungar (USA, 1957)	Phenformin introduced
Parke-Davis (1997)	Troglitazone, first thiazolidinesione introduced
Eli Lilly (2005)	Exenatide, first GLP-1 receptor agonist introduced
MSD (2007)	Sitagliptin, first DPP-4 inhibitor introduced
Janssen (2013)	Canagliflozin, first SGLT2 inhibitors
Diabetic monitoring and treatment targets	
University Group Diabetes Program (USA, 1969)	First randomized trial in diabetes
Peter Sönksen and Robert Tattersall (1978)	Introduction of self-blood glucose monitoring
R. Flückiger and K.H. Winterhalter (Germany, 1975)	Showed that HbA_{1c} was glycated haemoglobin
World Health Organization (1991)	St. Vincent Declaration identified targets for diabetes care
James Scott; Exactech (England, 1991)	First direct electronic glucose testing [64]

(*continued*)

Table 1.4 (*Continued*)

Diabetes Control and Complications Trial (USA, 1993)	Proved that improved glycaemic management prevents and slows progression of microvascular complication in type 1 diabetes
UK Prospective Diabetes Study (UK, 1998)	Proved that improved glycaemic and blood pressure management improve microvascular and macrovascular outcomes in type 2 diabetes
Steno-2 study (Denmark, 1999)	Multiple risk factor interventions improve outcomes [65]
UK Prospective study 10-year follow-up (UK, 2008)	Early treatment legacy effects [66]
Complications	
Wilhelm Manz (Germany, 1876)	Described *Retinitis proliferans*
Gerd Meyer-Schwickerath (Germany, 1964)	First use of Xenon photocoagulation
University of Minnesota Team (USA, 1966)	First combined kidney–pancreas transplants
John A. Hartford Foundation (USA, 1968)	Argon laser therapy [67]
Carl Erik Mogensen and Hans-Henrik Parving (Denmark, 1980s)	Strict blood pressure controls slows progression of diabetic neuropathy
EMPA-REG trial (2015)	SGLT-2 inhibitors ameliorate heart failure and cardiovascular disease [68]
LEADER trial	GLP-1 receptor agonists ameliorate cardiovascular disease [69]
CREDENCE trial	SGLT-2 inhibitors ameliorate chronic kidney disease [70]
Surgical approaches	
SOS study (Sweden, 2013)	Demonstrated resolution of diabetes with gastric by-pass surgery [71]

DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; SGLT, sodium-dependent glucose cotransporters.

These and other studies raised questions about whether lowering blood glucose levels to normal could prevent diabetes-related complications or reverse them once they had appeared. The hypothesis remained untestable for four more decades, until the means to achieve optimal glycaemic levels and measure them had been devised.

Insulin

For the first decade after its discovery, insulin was available only in its soluble (regular) formulation, whose short-action profile required multiple daily injections. The first delayed-action preparation, protamine insulinate, was introduced in 1936 by Hans Christian Hagedorn at Steno Diabetes Center in Denmark (Figure 1.17) [74]. This was followed by protamine zinc insulin later the same year, then globin insulin in 1939, NPH (neutral protamine Hagedorn, or isophane) in 1946, and the lente series in 1952. Long-acting insulins were welcomed by diabetes specialists and people with diabetes, but their use as a single daily injection probably produced worse glycaemic levels than three or four

Figure 1.17 Hans Christian Hagedorn (1888–1971) from the Hagedorn Medal. Source: Courtesy of C. Binder, Steno Diabetes Center Copenhagen, Denmark.

injections of soluble insulin. Indeed, delayed-action preparations were initially condemned by some diabetes specialists, such as Russell Wilder of the Mayo Clinic, because the person with diabetes could slip without apparent warning into hypoglycaemia.

The number and variety of insulin preparations proliferated, but the main advances were in methods to produce highly purified preparations from porcine or bovine pancreas, which remained the source for therapeutic insulin until the early 1980s. Insulin was the first therapeutic protein to be produced by recombinant DNA technology, initially by David Goeddel (*b.* 1951), who expressed synthetic genes encoding the A and B chains separately in *Escherichia coli* and then combined these chemically to produce human-sequence insulin [75]. From there, genetic engineering has been used to produce *designer* insulins such as the fast-acting insulin analogues lispro and aspart and the *peakless* basal insulins such as glargine, detemir, and degludec. These insulins are more expensive than NPH but the evidence suggests that there is less clinical hypoglycaemia with their use [76].

Most people with diabetes still inject insulin subcutaneously. Major milestones in its administration were the replacement of glass and steel syringes by disposable plastic syringes with fine-gauge needles, and then by *pen*-injection devices invented by John Ireland (1933–1988) in Glasgow in 1981 [77]. Portable insulin infusion pumps were developed by John Pickup (*b.* 1947) and colleagues in London during the late 1970s [78], and have become progressively smaller and more sophisticated. Both people with diabetes and manufacturers hope that there will eventually be an insulin that can be given without injection. The first inhaled insulin was marketed in 2006, although withdrawn a year later because of lack of demand and concerns about safety [79], but other products have reached the market more recently.

Other anti-diabetes agents

The first orally active glucose-lowering drug, synthalin, a guanidine derivative, was developed by Frank and colleagues in Breslau in 1926 [80], but had to be withdrawn because of toxicity (a recurrent problem for oral anti-diabetes drugs). The sulfonylureas originated from the work of Auguste Loubatières (1912–1977) in France

Figure 1.18 Dan Drucker, Joel Habener, and Jens Juel Holst – recipients of the Warren Alpert Prize (2020) and Canada Gairdiner Award (2021).

during the early 1940s on the glucose-lowering action of a sulfonamide derivative, 2254RP. Loubatières made the crucial observations that proved that these drugs act as insulin secretagogues and that they were effective in intact, but not in pancreatectomized, animals [81]. In 1955 carbutamide was the first sulfonylurea to enter clinical practice and tolbutamide followed in 1957. Phenformin, the first biguanide, was introduced in 1959 following research into the metabolic effects of guanidine derivatives that had built on Frank's initial studies [82]. Metformin appeared on the European market in 1960, but was not marketed in the USA until 1994. Troglitazone, the first of a class of anti-diabetes drugs – the glitazones or thiazolidinediones – was marketed in 1997 but withdrawn because of liver damage. It was followed by rosiglitazone and pioglitazone.

Another class of drugs, acting on the incretin system, was introduced in 2005. In 1986, Joel Habener (*b*. 1937) and Jens Juel Holst (*b*. 1945) simultaneously identified the amino acid sequence of biologically active, truncated glucagon-like peptide 1 (GLP-1), while Dan Drucker (*b*. 1956) described the first direct actions of GLP-1 on the β cell, specifically the glucose-dependent stimulation of insulin secretion and biosynthesis (Figure 1.18) [83]. Holst discovered the glucagon-suppressing and appetite-regulating effect of GLP-1 in humans. Importantly, the islet actions of GLP-1 are glucose dependent, making GLP-1 a safer treatment than sulfonylureas or insulin.

Today, long-acting GLP-1 receptor agonists are very effective treatments for hyperglycaemia in type 2 diabetes and highly efficacious for inducing weight loss. Inhibitors of the enzyme dipeptidylpeptidase-4 (DPP-4), which breaks down GLP-1 (gliptins), are also widely used. Oral versions of GLP-1 receptor agonists are now on the market.

In the 2010s another class of agents, the sodium-glucose cotransporter 2 (SGLT-2) inhibitors – the gliflozins – became widely available with action blocking the renal sodium-glucose cotransporters and thereby causing glycosuria; their effects were to lower plasma glucose, reduce blood pressure, and cause weight loss. A landmark trial using empagliflozin in high-risk people with existing cardiovascular disease showed a marked reduction in mortality [68].

Tolbutamide, phenformin, and insulin were compared in the treatment of *maturity-onset* diabetes in the first randomized controlled trial, the University Group Diabetes Program (UGDP) [84–86]. This much-criticized study concluded that the death rate was higher for both oral agents than for placebo, and that insulin (whether given in a fixed or variable dose) was no better than placebo [85]. The UGDP study, however, did not have correct randomization for pre-existing conditions such as myocardial infarction and its conclusions were uninterpretable and unsafe. Nevertheless, these findings were considered by some as suggesting that treatment of maturity-onset diabetes was a waste of time, a myth that was only laid finally to rest by the UK Prospective Diabetes Study (UKPDS) [87]. Beyond the UKPDS, there have been many cardiovascular outcome trials addressing separate issues relating to individual pharmacological agents.

Glucose management and treatment targets

During the 1920s, opinion leaders advocated normalizing blood glucose in young people with diabetes, the rationale being to *rest* the pancreas, in the hope that it might regenerate. The only way of monitoring the diabetes was by testing the urine for glucose, and attempts to keep the urine free from sugar inevitably resulted in severe hypoglycaemia and often psychological damage. This led to the so-called *free diet* movement – linked particularly with Adolf Lichtenstein (Stockholm) and Edward Tolstoi (New York) – which encouraged people with diabetes to eat whatever they liked and not to worry about glycosuria, however heavy. Tolstoi's view [88] was that a life saved by insulin should be worth living, and that people with diabetes should be able to forget that they had diabetes after each morning's injection; it seems likely that many physicians followed this policy for the next 40 years.

Adult physicians were similarly ambivalent about the importance of optimal glycaemic management. Only one-third of diabetes physicians questioned in England in 1953 thought that normoglycaemia would prevent diabetes-related complications, and only one-half advised urine testing at home [89].

Practical monitoring of diabetes management became feasible in the late 1970s with the introduction into clinical practice of test strips for measuring blood glucose in a fingerprick sample and the demonstration that most people with diabetes could use them at home [90, 91]. The discovery of haemoglobin A_{1c} by Samuel Rahbar (1929–2012) paved the way for glycated haemoglobin (HbA_{1c}) assays that gave an objective measure of overall glucose levels [92]. These methods in turn made possible the North American Diabetes Control and Complications Trial (DCCT), which in 1993 finally established that optimal glycaemic management prevents and delays the progression of microvascular complications in type 1 diabetes [93]. For type 2 diabetes, the importance of optimal glycaemic management was definitively proved by another landmark study, the UKPDS, masterminded in Oxford by Robert Turner (Figure 1.19). The UKPDS, which reported in 1998, not only showed a beneficial effect of improved glycaemic levels on microvascular complications [87], but also established the importance of treating hypertension [94]. By the late 1990s it was clear that lowering glucose levels, high blood pressure, or cholesterol separately would reduce the frequency of heart disease and death, and it was

Figure 1.19 Robert Turner (1939–1999), instigator of the UK Prospective Diabetes Study, the first study to show that optimal management of blood glucose and blood pressure was beneficial in type 2 diabetes. Source: Courtesy of the British Diabetic Association.

natural to wonder whether tackling them simultaneously (multiple risk factor intervention) would be even better. The Steno-2 study, which began at the Steno Diabetes Center in Copenhagen in 1992, enrolled people with type 2 diabetes with microalbuminuria, and after 13 years of follow-up showed that multiple risk factor intervention reduced the risk of death by 20% and the risk of developing nephropathy, retinopathy, and neuropathy by 50% [95].

Diabetes-related complications

Apart from the general benefits of improving blood glucose, some specific treatments have emerged for certain chronic complications. Well-conducted clinical trials during the late 1970s showed the effectiveness of laser photocoagulation in preventing visual loss from both maculopathy and proliferative retinopathy [96]. This technique was derived from the xenon arc lamp originally described in the late 1950s by Gerd Meyer-Schwickerath (1921–1992) of Essen, Germany [97].

The importance of blood pressure management in preventing the progression of nephropathy is now fully recognized, and blockade of the renin-angiotensin system may be particularly beneficial; Carl Erik Mogensen (*b*. 1938) and Hans-Henrik Parving (*b*. 1943) published studies in the early 1980s demonstrating that lowering blood pressure slowed the progression of nephropathy [98]. The detection of very low albumin concentrations in urine (microalbuminuria), now used throughout the world to screen for and monitor the course of diabetic nephropathy, is derived from a radioimmunoassay developed in 1969 by Harry Keen (1925–2013) and Costas Chlouverakis, at Guy's Hospital in London [99].

Diabetic ketoacidosis

The introduction of insulin was only one aspect of the management of this acute and previously fatal complication of diabetes. Of the first 33 cases treated by Joslin and his colleagues between 1 January 1923 and 1 April 1925, 31 survived – an excellent outcome, even by modern standards, which Joslin [100] attributed to 'Promptly applied medical care, rest in bed, special nursing attendance, warmth, evacuation of the bowels by enema, the introduction of liquids into the body, lavage of the stomach, cardiac stimulants, and above all the exclusion of alkalis'.

Sadly, other centres did not pay so much attention to detail. In 1933, the death rate from ketoacidosis in Boston was only 5%, but elsewhere in North America and Europe it averaged 30% and could be as high as 75%. An important advance in management was the acceptance of relatively low-dose insulin replacement, following the example of Ruth Menzel and colleagues in Karlsburg, Germany [101]. This broke with the tradition of high-dose regimens such as that proposed by Howard Root in the USA, which had recommended an average of 1200 units of insulin during the first 24 hours of treatment [102]. Another step forward was the recognition by Jacob Holler in 1946 of the danger of hypokalaemia [103]. Holler's observation helped to establish the need for monitoring plasma potassium levels, which became feasible with the introduction of the flame photometer and replacing potassium accordingly.

Diabetes in pregnancy

As late as 1950, the outcome of pregnancy in women with diabetes was still very poor in most units, with perinatal fetal losses of 45–65%, some 10 times higher than in the general population. Exceptions to this depressing rule were the units run by Priscilla White at the Joslin Clinic in Boston, who had published excellent results as early as 1935 [104], and by Jørgen Pedersen in Copenhagen (Figure 1.20). Pedersen identified the common features underpinning success as optimal glucose management and care provided by an experienced and dedicated team comprising a physician, obstetrician, and paediatrician [105]. Pedersen's target of a fetal mortality rate of 6% was not achieved in most European or US units until the 1980s.

Delivery of care for people with diabetes

From the earliest days of insulin injection and urine testing, it was apparent that people with diabetes needed knowledge and practical skills to manage their disease effectively. Lip service

(a)

(b)

Figure 1.20 (a) Jørgen Pedersen (1914–1978) and (b) Ivo Drury (1905–1988), pioneers, with Priscilla White (1900–1989), in the management of pregnancy in women with type 1 diabetes. Source: Courtesy of Dr Carl Erik Mogensen and the Royal College of Physicians of Ireland.

was often paid to the importance of diabetes education, but most individuals with diabetes were badly informed. In 1952, Samuel Beaser (1910–2005) questioned 128 people with diabetes attending the Boston Diabetes Fair, and found that 'all were distinctly deficient in knowledge of their disease' [106]; he felt that responsibility lay with both doctors and administrators. Further studies during the 1960s by Donnell Etzwiler (1927–2003) in Minneapolis showed that many doctors and nurses were also ignorant about managing diabetes. Since the 1980s, diabetes specialist nurses and nurse educators have been appointed in increasingly large numbers, thus fulfilling a suggestion originally made by Joslin in 1916.

National and international diabetes associations have also played an important part by supporting scientific and clinical research, providing practical and moral help for people with diabetes, and lobbying governments on their behalf. The first of these organizations was the Portuguese Association for the Protection of Poor Diabetics, founded in 1926 by Ernesto Roma of Lisbon after an inspiring visit to Joslin's clinic in Boston (Figure 1.21). The Association's aim was to provide free insulin and education for people with diabetes and their families. In the UK, the Diabetic Association (later the British Diabetic Association, and now Diabetes UK) was established in 1934 by Robin Lawrence of King's College Hospital, London, helped by the novelist H.G. Wells (Figure 1.21). Similar organizations were later founded in France (1938), the USA (1940), and Belgium (1942), and now exist in most countries.

On a wider scale, the American Diabetes Association (ADA) was founded in 1939, the International Diabetes Federation was established in 1950, and the European Association for the Study of Diabetes (EASD) in 1964. These organizations are devoted to the practice of diabetes care as well as the basic and clinical science of the disease, and have been valuable in coordinating treatment targets and strategies at international level; an important example was the St. Vincent Declaration, issued jointly in 1990 by the EASD and the World Health Organization [107].

(a)

(b)

Figure 1.21 (a) Ernesto Roma (1887–1978) and (b) Robin D. Lawrence (1892–1968). Source: Photograph of Dr Roma by courtesy of Manuel Machado Sá Marques and the Associação Protectura das Diabéticos de Portugal.

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Archives

The notebooks and personal papers of the discoverers of insulin are preserved at the Thomas Fisher Rare Book Library, University of Toronto, Canada.

2 Classification and Diagnosis of Diabetes

Ambady Ramachandran, Chamukuttan Snehalatha, Arun Raghavan, and Arun Nanditha

Dr. A. Ramachandran's Diabetes Hospitals and India Diabetes Research Foundation, Chennai, India

Key points

- Diabetes is a complex metabolic disease characterized by high levels of blood glucose and/or glycated haemoglobin (HbA_{1c}) resulting from defects in insulin secretion, insulin action, or both.
- There are three main types of diabetes and other less common specific types of diabetes with varied and overlapping aetiology.
- Although blood glucose remains the mainstay for the diagnosis of diabetes, HbA_{1c} is approved as an alternative diagnostic test for hyperglycaemia and in many countries is being increasingly used in place of glucose.
- Recent suggestions to classify diabetes according to β-cell defects may facilitate personalized, optimal therapy, but the diagnostic tests are too costly or unavailable in most laboratories.
- Varied diagnostic criteria for gestational diabetes are still being used.
- Impaired glucose tolerance (IGT) is a predictor of future type 2 diabetes and is also a cardiovascular risk factor.

Diabetes is one of the most common metabolic diseases with a complex, multifactorial aetiology and has varied clinical and biochemical manifestations. Multiple and varied therapeutic approaches are required for the glycaemic management of the different types of diabetes. The main pathological abnormalities of diabetes are an inadequate secretion and/or impaired action of insulin on target tissues. The severity of the resultant hyperglycaemia and the symptoms and signs vary widely. The development of diabetes-related microvascular complications depends largely on the degree and duration of hyperglycaemia.

Diabetes mellitus has been known since ancient times. The term *diabetes* was probably first used by Apollonius of Memphis around 250 BCE. The Latin word *mellitus* was added later, as the urine of people with diabetes was sweet and was used to distinguish diabetes mellitus from diabetes insipidus caused by defects in vasopressin [1].

Diabetes was described as early as 1500 BCE by Hindu scholars and Egyptian and Greek physicians as a mysterious disease causing emaciation and excess urination. If the urine tasted sweet, diabetes was diagnosed [2]. It was only in the 1800s that chemical tests were developed to detect the presence of sugar in the urine. The early descriptions were probably related to severe forms of the disease, either type 1 diabetes or overt type 2 diabetes.

In the late nineteenth century two categories were recognized: one category was described as occurring in young people with a short time course before ketoacidosis occurred, and the second one was described as common in older people and those with obesity. In 1936, Himsworth showed that diabetes could be divided into insulin-resistant and insulin-sensitive types, with the former being more common among older people [3].

Definition

Diabetes is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. Diabetes is distinguished by disturbances in carbohydrate, fat, and protein metabolism. The clinical symptoms include polyuria, polydipsia, polyphagia, weight loss, tiredness, and blurring of vision. With severe metabolic dysregulation, ketoacidosis or hyperosmolar non-ketotic coma may occur. However, symptoms may be mild or absent among people with type 2 diabetes for many years, especially when hyperglycaemia is minimal. Although the disease may remain undetected, tissue damage may develop and therefore diabetes-related complications may be present at the time of diagnosis [4,5]. Chronic hyperglycaemia may impair growth in children and increase the susceptibility to certain infections. In addition to the classic symptoms, people with diabetes may present with vague symptoms such as unexplained weight loss, fatigue, restlessness, and body pain.

Diabetes is associated with the development of long-term complications that can be divided into two main types. Microvascular complications include retinopathy (with potential loss of vision), nephropathy (leading to renal impairment), peripheral neuropathy (with risk of foot ulcers, amputations, or Charcot joints), and autonomic neuropathy (causing gastrointestinal, genitourinary, and cardiovascular symptoms, and sexual dysfunction) [4,5]. Macrovascular complications include cardiovascular diseases with increased incidence of atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular diseases as well as heart failure. Hypertension and dyslipidaemia often coexist in people with diabetes.

Textbook of Diabetes, Sixth Edition. Edited by Richard I.G. Holt and Allan Flyvbjerg.
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Diagnosis and classification of diabetes

Although variations in the presentation and course of diabetes have been known for many centuries, a clear distinction between two types of diabetes emerged only in the twentieth century. The first real attempt to classify diabetes was by the World Health Organization (WHO) Expert Committee on Diabetes Mellitus, which classified diabetes based on the age of onset of the disease into juvenile-onset diabetes and maturity-onset diabetes [6]. Although other phenotypes such as the brittle, gestational, pancreatic, endocrine, insulin-resistant, and iatrogenic varieties were described at that time, there was no clear understanding of the aetiology.

Blood glucose measurements became common, but no standard criteria for diagnosis were used. The diagnosis was usually made if there were clinical symptoms with high blood glucose levels and glycosuria. In juvenile-onset diabetes, ketonuria was noted to be common. Later on, with the availability of insulin measurement using radioimmunoassay, insulin deficiency or lack of insulin secretion in juvenile-onset diabetes and apparently normal or raised levels in maturity-onset diabetes could be demonstrated.

The WHO has published several guidelines for the diagnosis of diabetes since 1965 [5–7]. Its second report, published in 1980 [7], marked the beginning of the modern classification, which was a revision of the criteria published by the National Diabetes Data Group (NDDG) [8]. For the first time, four major groups were defined: insulin-dependent diabetes mellitus (IDDM, type 1); non-insulin-dependent diabetes mellitus (NIDDM, type 2); the 'other types'; and gestational diabetes mellitus. Two risk classes, previous abnormality of glucose intolerance and potential abnormality of glucose tolerance, were also suggested in place of the terms *pre-diabetes* or *potential* diabetes.

Both diagnosis and classification were reviewed in 1985 [9] and 1999 [5]. At the same time the American Diabetes Association (ADA) published a report of an expert committee on the diagnosis and classification of diabetes [10]. Both WHO and ADA classifications attempted to encompass both aetiology and clinical stages of the disease based on the suggestions of Kuzuya and Matsuda [11].

It was known that diabetes could progress through several clinical stages from normoglycaemia to ketoacidosis. With the discovery of human leucocyte antigen (HLA) and islet cell antibodies, it became clear that juvenile-onset diabetes or insulin-dependent diabetes had an autoimmune aetiology. Although maturity-onset diabetes was thought to be a *milder* form of the disease, it was recognized that people with type 2 diabetes could progress through varying levels of hyperglycaemia to a stage where insulin was required. By contrast, it was also possible to revert from a stage of requiring insulin to a point where normoglycaemia could be maintained through non-pharmacological intervention with modification of health behaviours, which is now termed *remission of diabetes*.

Methods and criteria for diagnosing diabetes

The criteria for the diagnosis of diabetes recommended by the ADA in 2021 [12] and approved by the WHO [13] and the International Diabetes Federation (IDF) are shown in Table 2.1.

Table 2.1 Criteria for the diagnosis of diabetes.

FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.
OR
2 h PG ≥200 mg/dl (11.1 mmol/l) during OGTT. The test should be performed, as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.
OR
HbA_{1C} ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP-certified and standardized to the DCCT assay.
OR
In a person with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/l).

In the absence of unequivocal hyperglycaemia, the diagnosis requires two abnormal test results from the same sample or in two separate test samples.
DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; NGSP, National Glycohemoglobin Standardization Program; OGTT, oral glucose tolerance test; PG, plasma glucose; WHO, World Health Organization.
Source: Reproduced from the American Diabetes Association Standards of Care 2021 [12].

Diagnostic thresholds

The thresholds for the diagnosis of diabetes are currently based on the glycaemic levels above which diabetes-related microvascular complications mostly occur. However, these thresholds have changed over time. The oral glucose tolerance test (OGTT) was first introduced by Hofmeister in 1889, but this was not standardized and various amounts of glucose with different two-hour thresholds were used throughout the 1960s and 1970s. The second WHO report published in 1980 [7] marked a breakthrough in harmonizing the diagnosis of diabetes. The report established that diabetes could be diagnosed with a casual plasma glucose of >11.0 mmol/l (200 mg/dl) or with a 75 g OGTT using fasting and two-hour thresholds of ≥8.0 mmol/l (145 mg/dl) and >11.0 mmol/l (200 mg/dl), respectively. The two-hour threshold was based on the observed risk of developing retinopathy in several populations, but there were less robust data for the fasting glucose threshold, which was later revised to the current value of 7.0 mmol/l (126 mg/dl).

In the development of diabetes, there is a stage when the blood glucose values are above normal, but below the thresholds used for defining diabetes, which is termed *pre-diabetes* or *intermediate hyperglycaemia*. Pre-diabetes encompasses abnormalities in fasting glucose (impaired fasting glycaemia) and two-hour post-glucose challenge glucose (impaired glucose tolerance, IGT). Both impaired fasting glycaemia and IGT increase the risk of developing diabetes, with approximately one-third of people with IGT developing type 2 diabetes; the annual incidence rate ranges between 2% and 10% depending on the population and the presence of risk factors [13]. Use of the term 'pre-diabetes' has been criticized on the basis that not all people with this condition progress to type 2 diabetes, and the term 'intermediate hyperglycaemia' is preferred by many. The diagnostic thresholds for pre-diabetes have also changed over time. The category of IGT was introduced by the WHO in 1965 and after a few iterations it was defined as a fasting glucose value of <7 mmol/l (126 mg/dl) and post-glucose value between ≥7.8 mmol/l (140 mg/dl) and

<11.1 mmol/l (200 mg/dl) [14]. The 1997 ADA and 1999 WHO criteria defined impaired fasting glucose (IFG) as a fasting glucose value between ≥6.1 mmol/l (110 mg/dl) and <7.0 mmol/l (126 mg/dl). In 2003, the ADA revised the lower cut-off value to ≥100 mg/dl (5.5 mmol/l). The reduction of normal fasting value to ≤100 mg/dl was partly to ensure that the prevalence of IFG was similar to that of IGT. Furthermore, many studies have shown that 5.6 mmol/mol (100 mg/dl) provides the best cut-point for predicting future diabetes and the level at which insulin secretion becomes abnormal. However, lowering this threshold significantly increases the prevalence of pre-diabetes, which has important personal and public health implications [15, 16]. As such, the WHO and other organizations did not adopt this change [15].

In 2011, glycated haemoglobin (HbA_{1c}) was also introduced as a further diagnostic criterion for diabetes, with a threshold of 6.5% (48 mmol/mol) [4, 17]. The HbA_{1c} test should be performed using the method certified by the National Glycohemoglobin Standardization Program or International Federation of Clinical Chemistry. A value of <6.5% (<48 mmol/mol) does not exclude diabetes diagnosed using glucose tests. The ADA report recognizes that individuals with an HbA_{1c} between 5.7% and 6.5% are at risk of diabetes and includes HbA_{1c} as a means of diagnosing pre-diabetes [17]. It should be noted that the risk of diabetes is continuous, can extend below the lower limit of the range, and is disproportionately greater at the higher end of the range [4].

Number of abnormal tests required

In an individual with classic symptoms of hyperglycaemia, only one measurement of glucose or HbA_{1c} above the diagnostic threshold is required to make the diagnosis. In the absence of a clear history of diabetes symptoms, however, the diagnosis of diabetes requires two abnormal test results from the same sample or in two separate test samples. Where there is uncertainty, the WHO and ADA recommend that a standard 75 g OGTT is used if possible in conjunction with HbA_{1c} measurement. However, clinical practice is changing and in many high-income countries, where procedures for the accurate measurement of HbA_{1c} are readily available, the OGTT is being used less and less frequently. In these settings, a single blood sample with measure of either fasting or random glucose and HbA_{1c} is more commonly used for the diagnosis.

Further considerations of method of diagnosis

When used on a population basis, fasting glucose, two-hour glucose, and HbA_{1c} identify slightly different groups of people as having diabetes. Thus, an individual may test positive for diabetes with one test but not another. As the OGTT combines both fasting and two-hour glucose, using fasting glucose alone will identify fewer people with diabetes than an OGTT. Studies in Asian populations [18] and the Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe (DECODE) study [19] showed that if only fasting blood glucose was used, nearly one-third of cases with diabetes might be missed at diagnosis. There are similar concerns about HbA_{1c}, but with time the groups coalesce to the point where all three tests become positive.

Analytical considerations

Blood glucose measurement has been the mainstay of diagnosis and monitoring glycaemic levels in diabetes for many decades. The OGTT is a comparatively inexpensive, sensitive index of hyperglycaemia including impaired glucose homeostasis. Standard enzymatic methods of glucose estimation are in widespread use.

Table 2.2 Advantages and limitations of using HbA_{1c}.

Advantages	Limitations
• Random sampling • Fasting not required • High sample stability • Negligible biological variability • Highly reproducible • Indicator of long-term glycaemic status • Single whole blood sample • Minimal assay variability and accuracy are assured when standard methods are used • Standardized across instruments • Guides physicians on the appropriate treatment • Predictive of development of vascular complications • Point-of-care tests are available in high-income countries	• Depends on changes in lifespan of erythrocytes • Genetic and ethnic variations • Affected by haemoglobinopathies • Affected by severe anaemia, hence may not be valid in people with chronic renal and liver diseases • May be unreliable in individuals with human immunodeficiency virus (HIV) • May not be valid in children, in older people, and in pregnancy • Assays are not standardized in many middle- and low-income countries • High cost • Lack of awareness among citizens and physicians in developing countries

However, high biological variability, poor reproducibility, and influence by acute factors such as stress, food, exercise, and some medications are the main disadvantages of using blood glucose. Moreover, precautions must be taken to reduce the lowering of sample glucose by glycolysis by adding anti-glycolytic agents, such as sodium fluoride. Despite this, the rate of decline in glucose concentration continues for up to four hours in small quantities. In addition, there are differences in glucose concentrations in whole blood, plasma and serum and between capillary and venous blood. The availability of point-of-care testing with glucometers has helped to reduce the disadvantages of blood glucose measurement to some extent. Moreover, rapid bedside measurements have also become possible with these meters.

HbA_{1c}, initially identified as an index of chronic hyperglycaemia, has now evolved into a valuable tool to monitor glycaemic management, for screening and diagnosis of diabetes and pre-diabetes, and as a predictor of micro- and macrovascular complications [20, 21]. Presently the results are traceable to the Diabetes Control and Complications Trial (DCCT) assay values (measured as %) [22] and can also be compared to the highly accurate International Federation of Clinical Chemistry (IFCC) standardized values (mmol/mol) [20]. Measuring HbA_{1c} has multiple advantages over blood glucose, but also has a few limitations, particularly in middle- and low-income developing countries (Table 2.2). Healthcare professionals using the test should be aware of these limitations and employ their discretion in interpreting the results [20, 23].

Classification of diabetes types

The aetiological classification of diabetes was described by the WHO [5] and also approved by the ADA [12]. The classification of type 2 diabetes is largely characterized by exclusion. The most recent WHO classification published in 2019 is shown in Table 2.3 [13].

As new causes are discovered they are included as 'other specific types', such as maturity-onset diabetes of the young (MODY).

Table 2.3 Classification of diabetes.

Type of diabetes	Brief description
Type 1 diabetes	β-cell destruction (mostly immune mediated) and absolute insulin deficiency; onset most common in childhood and early adulthood
Type 2 diabetes	Most common type, various degrees of β-cell dysfunction and insulin resistance; commonly associated with overweight and obesity
Hybrid forms of diabetes	
Slowly evolving, immune-mediated diabetes of adults	Similar to slowly evolving type 1 diabetes in adults, but more often has features of the metabolic syndrome, has a single glutamic acid decarboxylase (GAD) autoantibody, and retains greater β-cell function
Ketosis-prone type 2 diabetes	Presents with ketosis and insulin deficiency but later does not require insulin; common episodes of ketosis, not immune mediated
Other specific types	
Monogenic diabetes	
Monogenic defects of β-cell function	Caused by specific gene mutations; has several clinical manifestations requiring different treatment, some occurring in the neonatal period, others by early adulthood
Monogenic defects in insulin action	Caused by specific gene mutations; has features of severe insulin resistance without obesity; diabetes develops when β cells do not compensate for insulin resistance
Diseases of the exocrine pancreas	Various conditions that affect the pancreas can result in hyperglycaemia (trauma, tumour, inflammation, etc.)
Endocrine disorders	Occur in diseases with excess secretion of hormones that are insulin antagonists
Drug or chemical induced	Some medicines and chemicals impair insulin secretion or action, some can destroy β cells
Infection-related diabetes	Some viruses have been associated with direct β-cell destruction
Uncommon specific forms of immune-mediated diabetes	Associated with rare immune-mediated diseases
Other genetic syndromes sometimes associated with diabetes	Many genetic disorders and chromosomal abnormalities increase the risk of diabetes
Unclassified diabetes	Used to describe diabetes that does not clearly fit into other categories. This category should be used temporarily when there is not a clear diagnostic category, especially close to the time of diagnosis
Hyperglycaemia first detected during pregnancy	
Diabetes in pregnancy	Type 1 diabetes or type 2 diabetes first diagnosed during pregnancy
Gestational diabetes	Hyperglycaemia below diagnostic thresholds for diabetes in pregnancy

Source: Adapted from the World Health Organization Report, 2019 [13].

The WHO has revisited the classification several times with no major modifications. IGT was removed from the formal classification of type 2 diabetes, but was retained as a risk state. A new category of risk status, IFG, was introduced.

Type 1 diabetes

In most cases, type 1 diabetes occurs as a result of cellular-mediated autoimmune destruction of pancreatic β cells, causing an absolute deficiency of endogenous insulin. People with type 1 diabetes are dependent on exogenous insulin for survival and are ketosis prone. Markers of the immune destruction of the β cell include islet cell autoantibodies, autoantibodies to insulin, glutamic acid decarboxylase (GAD), and autoantibodies to the tyrosine phosphatases IA-2 and IA-2β. One or more of these autoantibodies are present in 85–90% of individuals when fasting hyperglycaemia is initially detected. The disease also has strong HLA associations, with linkage to the *DQA* and *DQB* genes, and is influenced by the *DRB* genes.

The rate of destruction of β cells is usually rapid in infants, young children, and adolescents and they often have ketoacidosis at the time of first presentation. Some people with type 1 diabetes, mostly adults, have a slower deterioration of β-cell function and show detectable levels of plasma C-peptide for many years. Type 1 diabetes is associated with other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, coeliac-sprue, autoimmune hepatitis, myasthenia gravis, and pernicious anaemia.

About 2–12% of people diagnosed with type 1 diabetes show phenotypic characteristics of type 2 diabetes at diagnosis and initially have glucose levels within target on oral anti-diabetes agents, before rapidly progressing to requiring insulin. They also show the presence of autoimmune markers of β-cell destruction, such as GAD autoantibodies. This subgroup was termed *latent autoimmune diabetes of adults* (LADA), but in the recent WHO classification the term LADA was removed because there was considerable controversy as to whether this was a separate condition to type 1 diabetes. It now comes under hybrid forms of diabetes with slowly evolving immune-mediated diabetes of adults [13].

A few people with type 1 diabetes may have no evidence of autoimmunity, but are prone to episodic ketoacidosis and may exhibit varying degrees of insulin deficiency and insulin dependency during those periods. This form, termed *idiopathic diabetes,* is commonly seen in people of African and Asian ethnicity and is strongly familial [4].

Type 2 diabetes

Type 2 diabetes constitutes more than 95% of the total population with diabetes. Its prevalence is increasing globally, but the most striking changes are now seen in low- and middle-income

countries. Type 2 diabetes may remain asymptomatic for many years and is undetected in nearly 50% of people affected by the disease [4, 5]. It is commonly diagnosed incidentally when a medical check-up is done for other reasons. Type 2 diabetes is characterized by a relative insulin deficiency; although there is insulin secretion, this is insufficient to overcome insulin resistance. Though many people with type 2 diabetes manage their diabetes with lifestyle changes alone, with time oral anti-diabetes agents are needed to maintain normoglycaemia, with many people eventually requiring insulin. Chronic exhaustion of β-cell function is a major cause of this.

Although research studies have focused on the molecular mechanisms underlying type 2 diabetes, only modest success has been achieved in unravelling the genetic abnormalities. In the past two decades, type 2 diabetes in children and adolescents has become common in Asian populations and could be partly attributed to the rising rates of obesity and changing lifestyle patterns [24]. A minority of people with type 2 diabetes are prone to episodes of ketosis. They have insulin deficiency but no immune markers. This hybrid form is termed ketosis-prone type 2 diabetes [13].

There has been a proposal to modify the classification of type 2 diabetes to identify people at increased risk of complications and support precision treatment by tailoring the type of therapy with greatest benefit for the individual with diabetes. Recently, a substratification in 8980 individuals with newly diagnosed diabetes was undertaken in Sweden using clusters based on six variables: GAD antibodies, age at diagnosis, body mass index (BMI), HbA_{1c}, and estimates of β-cell function and insulin resistance. The analysis was based on prospective data from medical prescriptions and development of complications from electronic records of the examined individuals [25]. Five clusters of phenotypes with distinct characteristics were identified. Individuals in cluster 1 (severe autoimmune diabetes) had early-onset disease, low BMI, relatively higher HbA_{1c}, insulin deficiency, and presence of GAD antibodies. Cluster 2 (severe insulin-deficient diabetes) was GAD antibody negative, with low age at onset, low BMI, low insulin secretion, and relatively higher HbA_{1c}. Cluster 3 (severe insulin-resistant diabetes) had high insulin resistance and high BMI, while cluster 4 (mild obesity-related diabetes) had obesity but not insulin resistance. Cluster 5 (mild age-related diabetes) was older but was similar to cluster 4 with modest metabolic derangements. Among these the highest percentage (39.1%) was cluster 5 and the lowest cluster 1 (6.4%).

The clusters had varied dispositions to specific complications of diabetes such as kidney disease, coronary events, and stroke. Clusters 1 and 2 had a higher HbA_{1c} at diagnosis than the other clusters and a higher frequency of ketoacidosis. Cluster 2 had the highest risk of retinopathy, and cluster 3 had the highest prevalence of non-alcoholic fatty liver disease and chronic kidney disease. Cluster 4 had an increased risk of diabetes kidney disease and cluster 5 appeared to have a lower risk of renal disease.

The authors suggested that further improvement in the stratification may be possible through the inclusion of additional variables such as biomarkers, genotypes, or genetic risk scores. Therefore, the study suggested the superiority of identifying the new clusters during classification, which will possibly provide better guidance for appropriate treatment regimens. However, the tests required for identifying the clusters are costly and are available only in a limited number of advanced research institutions and hospitals. More detailed clinical trials are required to confirm the utility of this classification.

Other specific types

These forms of diabetes are relatively less common. The underlying defects of the disease processes can be identified in these forms, such as those listed in Table 2.3. Some of these defects are remediable and the diabetes can be cured [4, 5].

Gestational diabetes

For many years, gestational diabetes was defined a state of carbohydrate intolerance resulting in hyperglycaemia of variable severity, with onset or first recognition during pregnancy. It does not exclude the possibility that the glucose intolerance may antedate pregnancy but has previously gone unrecognized. The definition applies irrespective of whether or not insulin is used for treatment or whether the condition persists after pregnancy [12, 13]. According to this definition, gestational diabetes may develop at any stage of pregnancy, but many now consider diabetes detected during the first trimester of pregnancy to be previously undiagnosed pre-existing diabetes. The term gestational diabetes is then reserved for diagnoses made in the second or third trimester of pregnancy. Women who have diabetes and subsequently become pregnant are termed as having *diabetes mellitus and pregnancy* and should be treated accordingly during and after the pregnancy. This is discussed in greater detail in Chapter 71. The International Association of Diabetes and Pregnancy Study Groups' (IADPSG) criteria for diagnosis of gestational diabetes are shown in Table 2.4 [27]. These criteria have been adopted by main national guidelines, including

Table 2.4 Screening for and diagnosis of gestational diabetes.

One-step strategy

Perform a 75 g OGTT, with plasma glucose measurement when the individual is fasting and at 1 h and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with diabetes. The OGTT should be performed in the morning after an overnight fast of at least 8 h. The diagnosis of gestational diabetes is made when any of the following plasma glucose values are met or exceeded:

- Fasting: 92 mg/dl (5.1 mmol/l)
- 1 h: 180 mg/dl (10.0 mmol/l)
- 2 h: 153 mg/dl (8.5 mmol/l)

Two-step strategy

Step 1: Perform a 50 g GLT (non-fasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in women not previously diagnosed with diabetes. If the plasma glucose level measured 1 h after the load is ≥130, 135, or 140 mg/dl (7.2, 7.5, or 7.8 mmol/l, respectively), proceed to a 100 g OGTT.

Step 2: The 100 g OGTT should be performed when the individual is fasting. The diagnosis of gestational diabetes is made when at least two[a] of the following four plasma glucose levels (measured fasting and at 1, 2, and 3 h during OGTT) are met or exceeded:

- Fasting: 95 mg/dl (5.3 mmol/l)
- 1 h: 180 mg/dl (10.0 mmol/l)
- 2 h: 155 mg/dl (8.6 mmol/l)
- 3 h: 140 mg/dl (7.8 mmol/l)

GLT, glucose load test; OGTT, oral glucose tolerance test.

[a] American College of Obstetricians and Gynaecologists notes that one elevated value can be used for diagnosis [26].

Source: Adapted from American Diabetes Association, 2021 [12].

those of the ADA, but not by all countries [12]. Establishing a uniform approach to diagnosis will have extensive benefits for women, caregivers, and policy makers.

Women with any of the following risk factors should be screened with an appropriate blood test as shown in Table 2.4, during the first prenatal visit; if the result is found to be normal, they should be tested again between 24 and 28 weeks of pregnancy [12, 13]. The risk factors for gestational diabetes include older age, obesity (BMI >30 kg/m^2), history of elevated blood glucose levels or gestational diabetes during previous pregnancy, women who have large-for-gestational age babies, a strong family history of diabetes, and women from high-risk ethnic groups such as Asians [28].

Hyperglycaemia may resolve after the delivery, but 5–10% of women may continue to have diabetes, most often type 2 diabetes. These women require treatment with lifestyle changes and appropriate anti-diabetes agents. Women with gestational diabetes should be screened for diabetes immediately postpartum and again at 6–12 weeks postpartum using non-pregnant OGTT criteria [29]. HbA_{1c} cannot be used in the immediate postpartum period, but is an effective alternative way of screening for persistent glucose abnormalities from 12 weeks postpartum where the facilities for accurate measurement are available. Women with gestational diabetes are at risk of future diabetes outside pregnancy and should be offered screening on an annual basis. Women who show impaired glucose regulation at this stage should be treated with lifestyle interventions and in some circumstances metformin.

Conclusion

The advances made in the past two decades in diagnostic and research methodologies for identifying pathophysiological components of various types of diabetes have provided significant clarity in the classification and diagnosis of diabetes [26]. This has helped to establish some uniformity in data collection and has also allowed comparison of the international profile of the disease. Consensus in establishing diagnostic criteria for gestational diabetes is lacking. Emphasis should be given to identifying the pre-diabetes states that are the strongest predictors of incident type 2 diabetes.

The classification of diabetes should facilitate optimal personalized diabetes care. There are many diabetes subtypes, especially among type 2 diabetes, type 1 diabetes, and the autoimmune type of diabetes. The current state of knowledge suggests that the classification should be based on β-cell pathology contributing to β-cell dysfunction [30]. At present, the facilities for specialized analysis required for such a classification, such as genotyping and advanced immune pathology, are available only in a few advanced specialized research laboratories and are too costly [31, 32]. Nevertheless, the classification of diabetes continues to evolve as underlying genetic and other factors become identified with increasing precision.

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3 The Global Burden of Diabetes

Jessica L. Harding[1,2,3], Mary Beth Weber[4,5], and Jonathan E. Shaw[6,7,8]

[1] Department of Medicine, School of Medicine, Emory University, Atlanta, GA, USA
[2] Department of Surgery, School of Medicine, Emory University, Atlanta, GA, USA
[3] Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA
[4] Global Diabetes Research Center, Rollins School of Public Health, Emory University, Atlanta, GA, USA
[5] Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA
[6] Clinical and Population Health, Baker Institute, Melbourne, Australia
[7] School of Life Sciences, La Trobe University, Melbourne, Australia
[8] School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia

Key points

- Diabetes results in a range of distressing symptoms, altered daily functioning (requiring attentive self-care, health monitoring, and treatments), changed family roles, higher healthcare costs, lost productivity, disability, and premature mortality, which are felt by individuals, households, communities, and national economies.
- The prevalence of diabetes has grown worldwide, with no country or region spared. Concerningly, estimates of prevalence and absolute numbers of people living with diabetes have consistently outpaced each previous projection. Projections for 2045 suggest that the greatest increases will be seen in low- and middle-income countries.
- In contrast, evidence from predominantly high-income countries suggests that diabetes incidence may have started to decline in more recent years.
- Diabetes is a leading cause of death in the world with 4.2 million deaths annually, equivalent to one death every eight seconds. Diabetes-related mortality disproportionately affects low- and middle-income countries, the young, and economically active populations.
- Declining mortality among people with diabetes will increase the total years of life spent living with diabetes and may drive the emergence of *new* diabetes-related complications such as cancer, mental health disorders, cognitive impairment, and disability. A longer life lived with diabetes may also exacerbate the risk of established diabetes macrovascular and microvascular complications, as well as infections, including the newly emerged Covid-19.
- In 2019, the global direct health expenditure of diabetes was estimated to be US $760 billion and is expected to grow substantially in the coming decades. The majority of this spending (~90%) is in high-income countries, despite a greater absolute diabetes burden in low- and middle-income countries, exacerbating existing disparities between high-income countries and low- and middle-income countries.
- Diabetes impairs one's ability to perform domestic and occupational activities. Decreased workplace productivity, impaired interpersonal relationships, and perceived discrimination can impede diabetes self-management and affect an individual's ability to integrate fully into society.
- Preparation for the increasing diabetes burden requires progress in the wider collection of reliable data in a standardized manner across various countries. In particular, there is a current scarcity of data from low- and middle-income countries regarding diabetes-related mortality, complications, disability, and costs.
- Confronting the increasing burden of diabetes, particularly in vulnerable subpopulations, will require addressing the underlying political, social, cultural, behavioural, and economic factors that impede the translation of known effective strategies to reduce diabetes risk in the population.

Diabetes is one of the fastest-growing health challenges of the twenty-first century. The number of adults living with diabetes has more than tripled over the past 20 years, with serious health-related and socioeconomic impacts on individuals and populations alike. Pandemic growth of diabetes is spurred on by transitioning demographic (e.g. population ageing), nutritional, and lifestyle patterns, and an affiliated proliferation of overweight and obesity in adults and children [1–3]. The International Diabetes Federation (IDF) estimated that there were 463 million people with diabetes worldwide in 2019 and projects that the absolute number will reach 700 million by 2045 if current trends persist [1]. The overwhelming majority of this escalation will be attributable to an increase in type 2 diabetes, with the greatest impact expected in low- and middle-income countries (LMIC) due to rapid socioeconomic and lifestyle transformations [4–6].

Current estimates suggest that three-quarters of those affected by diabetes live in LMIC [1,7]. This challenges previously held paradigms that distinguished chronic non-communicable diseases as problems of affluent countries alone. Although the greater absolute burden of diabetes may be partially explained by the larger population size of LMIC, the growth rates for non-communicable diseases in rapidly transitioning LMIC are much higher than those in more

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affluent high-income countries (HIC) [8]. For example, it was previously estimated that by 2025, the number of people with diabetes will increase by 170% in LMIC, compared with a 41% increase in HIC [9].

Thus far, the attention on health burdens in LMIC has justifiably focused on the persistence of infectious diseases, reproductive health problems, and nutritional deficiencies. However, these same countries must also contend with 80% of the global mortality associated with chronic diseases [10, 11]. Projections suggest that this already overwhelming 'double burden' will be exacerbated by the further growth of non-communicable diseases such as diabetes. Altogether, projected increases in diabetes in all corners of the world will result in a corresponding escalation of burdens in the form of serious morbidity, disability, diminished life expectancy, reduction in quality of life, loss of human and social capital, and individual and national income losses. This chapter describes these burdens in a global context, and systematically introduces data regarding regional patterns and associated themes.

Prevalence

In recent decades, large increases in diabetes prevalence have been demonstrated in virtually all regions of the world, largely attributed to a rise in type 2 diabetes and its risk factors. In 2019, 1 in 11 adults aged 20–79 was living with diabetes (463 million people), of whom 79% were living in LMIC [1]. Quantification of the prevalence of diabetes is important for healthcare planning and resource allocation and facilitates the formulation of appropriate disease prevention and control strategies. However, there are still insufficient representative and rigorous epidemiological data from many LMIC to reliably capture the true global diabetes burden. Moreover, the utility of currently available estimates is hampered by methodological deficiencies (e.g. inconsistent diagnostic criteria, poor standardization of methods) and limited coverage (e.g. regional sampling with a predominance of urban studies even though many of the populations in question have large numbers of rural inhabitants) [12, 13]. To address these barriers, the IDF and World Health Organization (WHO) use sophisticated modelling approaches to provide global estimates, by country, for diabetes prevalence. In the following, we highlight notable patterns in the three most common types of diabetes, type 1 diabetes, type 2 diabetes and gestational diabetes mellitus (GDM), and compare estimates by different income-group regions.

Type 1 diabetes

The prevalence of type 1 diabetes is increasing worldwide due to a combination of improved survival and an increase in incidence, thought to be driven by environmental and lifestyle-related changes [14], such as rapid weight gain and/or inappropriate feeding in infancy [15, 16]. In 2019, the number of children and adolescents aged 0–14 years and 0–19 years with type 1 diabetes was 600 900 and 1.1 million worldwide, respectively, with a large proportion residing in Europe and North America where incidence continues to increase [17–19] (Table 3.1). India, the USA, and Brazil have the largest numbers of children and adolescents living with type 1 diabetes, with 95 600, 94 200, and 51 500, respectively, as of 2019.

The prevalence of type 1 diabetes in adults is less well known and estimates typically rely on self-reporting of diabetes type and treatment status, thus are limited in their ability to accurately distinguish between type 1 and type 2 diabetes in adults [20, 21]. Consequently, a global perspective on the prevalence of type 1 diabetes in adults remains elusive.

Type 2 diabetes

In 2019, it was estimated that 9.3% of all adults aged 20–79 years (463 million) were living with diabetes, with the majority assumed to be type 2 diabetes. This is projected to increase to 10.9% (700.2 million) in 2045, with the greatest increases expected to be seen in LMIC. Age-adjusted comparative prevalence estimates are shown in Table 3.1 and vary by region, whereby the highest prevalence is seen in the Middle East and North Africa regions. The countries with the largest absolute number of adults aged 20–79 years with diabetes are China (116 million), India (77.0 million), and the USA (31 million), though countries with the highest age-adjusted prevalence of diabetes include some Pacific islands, Pakistan, Sudan,

Table 3.1 Estimated numbers of children and adolescents with type 1 diabetes and prevalence of type 2 diabetes in adults and gestational diabetes mellitus (GDM; hyperglycaemia in pregnancy) in pregnant women by region.

	Type 1 diabetes	Type 2 diabetes	GDM
Region	Number of children and adolescents (0–14 yr) with type 1 diabetes (in thousands)	Age-adjusted prevalence (%) and 95% confidence interval (CI) among adults aged 20–79	Age-adjusted prevalence (%) of GDM, and numbers of births (millions) among pregnant women
Africa	10.0	4.7 (3.2–8.1)	9.6 (3.5)
Europe	162.6	6.3 (4.9–9.2)	16.3 (2.0)
Middle East and North Africa	82.0	12.2 (8.3–16.1)	7.5 (1.9)
North American and Caribbean	121.4	11.1 (9.0–14.5)	20.8 (1.6)
South and Central America	69.0	8.5 (6.7–11.3)	13.5 (1.0)
South-East Asia	100.0	11.3 (8.0–15.9)	27.0 (6.6)
Western Pacific	56.0	11.4 (8.3–15.6)	12.3 (3.8)
World	**600.9**	**8.3 (6.2–11.8)**	**14.4 (20.4)**

Source: Data sourced from the 2019 IDF Diabetes Atlas [1].

and other countries in the Middle East and North Africa. National prevalence estimates of 15–30% are reported in these countries.

The prevalence of type 2 diabetes also varies considerably between subpopulations within countries or regions. For example, in established market economies, those in lower socioeconomic groups (e.g. lower education, lower income) have a higher burden of diabetes relative to higher socioeconomic groups. In LMIC regions, the prevalence of diabetes typically remains lower in lower and middle socioeconomic classes; however, these groups tend to make up a larger proportion of the overall population and thus the absolute number of people affected by diabetes in these social groups is much higher than in their wealthier counterparts [22, 23]. Further, there are major differences in prevalence between ethnic groups. For example, both Hispanic and Asian populations have a higher prevalence of diabetes compared with European and sub-Saharan African populations [24, 25]. This is likely due to multiple factors, including genetic, epigenetic, lifestyle, and environment. More epidemiological data, especially from longitudinal studies, are needed to inform our understanding of pathophysiology, and studies are required to determine best practices and describe effective interventions to screen, prevent, and manage diabetes in country-specific settings. The following are some notable examples of within-country and within-region variations based on available data. The regions are based on groupings used by the IDF.

Sub-Saharan Africa

- Diabetes prevalence varies considerably between countries in this region, with age-adjusted prevalence estimates ranging from a low of 1.0% in Benin to a high of 12.7% in South Africa [1]. There is also great variability in rural versus urban prevalence, with urban areas facing the brunt of the burden [26–28]. The wide variation in diabetes prevalence may be explained partly by regional differences in lifestyle and body mass index (BMI).
- A higher prevalence of diabetes has been noted among people of Egyptian and Asian Indian origin as compared with Indigenous African people [13, 29].
- Data on diabetes prevalence in sub-Saharan Africa originate from just a few localized centres in certain parts of the continent, and estimates vary widely, between 0% and 3% in rural areas and 6% and 12% in urban environments [13, 30]. Further, data on population-level dietary and physical activity patterns, suspected to be key drivers leading to an increase in diabetes, are severely lacking in African countries.
- As human immunodeficiency virus (HIV) mortality declines through widespread uptake of anti-retroviral therapies, the direct (e.g. pancreatic dysfunction associated with therapy) and indirect (e.g. increased life expectancy) effects are likely to have an impact on diabetes prevalence [31].

Europe

- Across 56 countries that vary markedly in size, language, ethnic groups, and affluence, the age-adjusted prevalence ranges from 2.1% in Greenland to 11.1% in Turkey [1].
- Structural deprivation may explain part of the regional differences, along with individual socioeconomic status and ethnic mix [32, 33].

Middle East and North Africa

- The Middle East and North Africa region has some of the highest age-adjusted diabetes prevalence estimates in the world, ranging from 5.4% in Yemen to 22.1% in Sudan [1].
- The Gulf region has experienced an especially marked and sudden increase in rates of diabetes, where Kuwait (12.2%), Saudi Arabia (15.8%), and Bahrain (15.6%) now rank among the countries with the highest prevalence of type 2 diabetes worldwide [1].

North America and Caribbean

- Diabetes prevalence is, generally, higher in Caribbean than in North American countries, with age-adjusted estimates ranging from 6.6% in Haiti to 14.2% in the British Virgin Islands (vs 7.6% in Canada and 10.8% in the USA) [1].
- In the USA, the variations by race and ethnicity have been extensively described, with ethnic minorities more likely to have a higher burden of diabetes. For example, a 2019 study demonstrated that among adults, the prevalence was 12.1%, 20.4%, 22.1%, and 19.5% in adults of white European, non-Hispanic Black, Hispanic, and non-Hispanic Asian ancestry, respectively [34].
- In Canada and the USA, diabetes prevalence is considerably higher in Indigenous than in non-Indigenous groups. In Canada, First Nations people living on reserve have an age-adjusted prevalence of 17.2% compared to 10.3% among First Nations living off reserve, and 5.0% among non-Indigenous Canadians [35]. The US Pima Indians have the highest prevalence of type 2 diabetes in the world, with 34.2% for Pima men and 40.8% for Pima women (compared to 9.3% in the calendar year–matched general US population) [36].
- Life expectancy of people with diabetes in North America, although reduced compared with the general population [37], is markedly higher than in LMIC.

South and Central America

- The average age-adjusted prevalence of diabetes is 8.5%, but ranges from 5.5% in Ecuador to 13.7% in Puerto Rico [1], reflecting the diversity of ethnicities and stages of development between countries [7].
- Indigenous populations are estimated to have a high prevalence of metabolic dysfunction and diabetes, as has been noted in Brazil [38], but the patterns and proportions of Indigenous peoples in each country are not clearly documented [39].

South-East Asia

- The age-adjusted prevalence ranges from 7.2% in Nepal to 22.0% in Mauritius [1].
- South-East Asian adults are confronted with diabetes risk being manifest at younger ages and at lower BMIs compared with populations in other regions [40], possibly due to lower insulin secretion and a greater tendency for deposition of metabolically active visceral adiposity [41–43].
- Rural–urban differences in prevalence of diabetes among Asians suggests genetic, and environmental factors, and their interactions all have a role to play [44].

Western Pacific

- The age-adjusted prevalence ranges from 3.9% in Myanmar to 30.5% in the Marshall Islands [1].
- Indigenous populations in Australian and New Zealand, similar to those in Canada and the USA, are disproportionally burdened by diabetes. In Australia and New Zealand, Indigenous [45] and Māori and Pacific [46] peoples are three times more likely to have diabetes compared to their non-Indigenous counterparts.
- In China, rural areas have historically had a lower prevalence of diabetes compared with urban areas. However, a 2020 study reported that diabetes prevalence in rural regions has increased at a

rate 2.5 times that of urban areas (between 2013 and 2017 [47, 48]), such that prevalence estimates are now similar in rural and urban areas (12.0% and 13.7%, respectively) [47].

To prevent diabetes-related complications such as nerve, eye, kidney, and/or vascular diseases, type 2 diabetes should be diagnosed as early as possible [49–51]. Yet in 2019, 50% of the 463 million adults living with diabetes were unaware that they have the condition [1]. The slow progression and lack of symptoms in the early stages of disease often delay people seeking a glucose test, preventive care, and/or medical attention. Perhaps unsurprisingly, the proportion of diabetes that remains undiagnosed is much higher in low-income than in middle-income countries (75% vs 46%, respectively) [52]. Overall, it is estimated that 84% of all cases of undiagnosed diabetes are in LMIC, with Pacific Island nations showing the highest prevalence of undiagnosed diabetes [53]. These estimates point to an urgent need for developing and improving diabetes screening programmes.

Gestational diabetes mellitus

The prevalence of GDM, one of the most common pregnancy complications, has increased by more than 30% within one or two decades in several countries, including some developing countries [54]. Some of this increase is likely related to changes in diagnostic criteria. In 2019, an estimated 15.8% (20.4 million) of live births were affected by hyperglycaemia in pregnancy, of which 83.6% were due to GDM [1]. The prevalence of GDM increases with age: 37.0% of women aged 45–49 years have GDM compared with 10.1% in women aged 20–24 years. There are also regional differences in age-adjusted GDM: 27.0% of live births in South-East Asia compared with just 7.5% in the Middle East and North Africa (Table 3.1) [1]. More than 85% of women with GDM are seen in LMIC where access to antenatal care is often limited.

In the USA, Canada, and Australia, there are notable differences in the racial/ethnic-specific prevalence of GDM. For instance, in the USA, prevalence varies from 4.5% to 10.9% in non-Hispanic white compared to Filipina women [55]. In Australia, women of South Asian origin are more than four times as likely to develop GDM compared to their Australia/New Zealand–origin counterparts [56]. The reasons underlying the racial/ethnic differences are yet to be elucidated, but the mechanisms could be multifaceted, including differences in body composition, lifestyle (diet and physical activity), acculturation, genetic susceptibility, cultural beliefs and practices around prenatal behaviours, and healthcare systems and reporting practices [57].

Incidence of type 2 diabetes

Much of the epidemiology of type 2 diabetes has been described in terms of its prevalence and of the total numbers of people affected. This provides an excellent assessment of the population-level burden and can identify subgroups of the population who are more susceptible to diabetes. Within this framework of data, changing prevalence of diabetes over time is typically interpreted as changing risk for diabetes in the population. If the prevalence of diabetes rises, it is often assumed that lifestyle or other risk factors are deteriorating, leading to an increase in diabetes risk and an assumption that perhaps measures to reduce risk have failed. However, the prevalence of diabetes, like that of any other condition, is determined by two factors – the rate at which people develop the condition and the rate at which people leave the condition. The former is the disease incidence and the latter comprises mortality, migration, and cure (or remission).

It is clear from this brief discussion that the prevalence of diabetes can rise simply because of falling mortality. Indeed, even if the incidence of diabetes is falling, it is possible that prevalence will rise, so long as the number of new cases each year exceeds the number of people with diabetes who die each year. Thus, in settings where the treatment of diabetes and related conditions is improving and mortality is falling, changes in the prevalence of diabetes may not accurately reflect changes in population risk. Incidence, however, is defined as the number of new cases arising within a disease-free population each year and is a much more direct measure of the population risk of diabetes than is prevalence. Therefore, assessments of population risk can only be reliably made from incidence studies, and only changes in incidence over time can be used to definitively infer changes in population risk.

Unfortunately, incidence studies can be difficult to conduct. The classic prospective cohort study is typically small and with only modest response rates, limiting generalizability and the ability to derive precise incidence estimates. Furthermore, such studies cannot easily be used to track changes in incidence over time. As a result, the population-level descriptions of diabetes epidemiology have remained focused on prevalence, despite the issues described above.

In recent years, analyses based on much larger data sources, such as registries and electronic health records, have started to fill this gap. These analyses often include whole populations and therefore can generate precise estimates, as well as limit selection biases. They are not, however, without limitations. For example, it is often difficult to standardize diagnostic approaches, as the data are collected through clinical practice rather than via research protocols. Furthermore, they give no measure of undiagnosed diabetes, and so can be influenced by changes in screening and diagnostic behaviour. Nevertheless, current incidence data from such sources provide an important addition to prevalence data and have already suggested a different pattern to that indicated by examining prevalence studies.

A recent systematic review of published studies reporting trends in the incidence of type 2 diabetes or total diabetes over time identified 47 relevant publications, and found that between 2006 and 2014 two-thirds of populations experienced either a stable or declining incidence of diabetes [58]. This contrasted with the period from 1990 to 2005, during which diabetes incidence rose in two-thirds of populations [58]. A subsequent analysis of new data from administrative datasets in over 20 countries, representing 5 billion person-years of follow-up, had similar findings [59]. From 2010 onwards, 19 of 23 country-specific data sources had a downward or stable trend, with annual reductions in diabetes incidence ranging from 1.1% to 10.8%. In this analysis, data from two of the populations indicated that changes in diagnostic testing for diabetes (i.e. testing frequency and the use of HbA_{1c} instead of glucose) were unlikely to explain the observed declines in the incidence of diabetes [59]. These findings apply only to HIC and a small number of middle-income countries, reflecting the distribution of these data systems. Nevertheless, they indicate that, at least in some parts of the world, the incidence of type 2 diabetes may now be falling.

The reasons for a fall in incidence remain uncertain. Since administrative data only report on clinically diagnosed diabetes, it is possible that reductions in screening activity could play a role,

although there is no evidence that such a reduction has occurred. In some countries, but not others, the fall in incidence occurred at a similar time to the introduction of HbA_{1c} as a diagnostic test, though as already noted, where data were available this did not account for reductions in incidence. Aggressive screening programmes in the early 2000s may have depleted the pool of people with undiagnosed diabetes, leading to a rebound fall in new clinical diagnoses thereafter. However, since the pool of people with undiagnosed diabetes is continually replenished as people age, such a rebound fall might be expected to be short-lived. This leaves the possibility that the huge public health and clinical focus on reducing the risk of developing type diabetes might have had some effect.

Trends in diabetes-related complications

Global increases in diabetes prevalence, predominantly type 2 diabetes, will increase the number of chronic and acute diabetes complications in the general population, with profound effects on quality of life, demand on health services, and economic costs. Macrovascular complications of diabetes, including coronary heart disease, stroke, and peripheral artery disease, and microvascular complications, such as end-stage renal disease, retinopathy, and neuropathy, along with lower-extremity amputations, a common consequence of peripheral artery disease and neuropathy, are responsible for much of the burden associated with diabetes. There is also growing recognition of a diversifying set of causally linked conditions, including cancers, ageing-related outcomes (e.g. dementia), infections, and liver disease. Since rates of all-cause and cardiovascular disease mortality are decreasing in individuals with diabetes [60–63], other complications of diabetes may become proportionately more prominent in the future.

Understanding the burden of diabetes-related complications is crucial for understanding the overall health burden associated with diabetes and provides important context to concurrent changes in the prevalence of diabetes. However, despite widespread international assessment of the growth of diabetes prevalence, quantification of the international burden and variation in the incidence of diabetes-related complications is notably lacking. This stems largely from the fact that data systems and population-based studies assessing diabetes complications are concentrated in Europe, North America, and other HIC in the Asia-Pacific region, with little to no availability in LMIC, leaving the global status of diabetes complication rates unclear. This gap in data stems largely from the lack of population-based systems quantifying healthcare utilization, because surveys and cohort studies are generally inadequate for the assessment of diabetes-related complications. The lack of both uniform diagnosis of diabetes and of standardized measurement of diabetes-related complications has caused additional barriers in comparing trends worldwide. In the following, we highlight notable patterns in several diabetes-related complications and, where possible, regional variations.

Macrovascular complications

Macrovascular, or cardiovascular disease, complications of diabetes include coronary artery disease (i.e. ischaemic heart disease, heart attack, sudden coronary death), cerebrovascular disease or stroke, and peripheral artery disease. People with diabetes have a two- to fourfold increased risk of cardiovascular disease [64, 65], and these events generally occur at an earlier age compared to people without diabetes [65]. As the number of people with diabetes is predicted to increase, it is expected that the number of people with cardiovascular disease will also increase. In studies of middle-aged (50–69 years) adults with diabetes living in high- and middle-income countries, up to 41% report a history of cardiovascular disease, and 2–27 people in every 1000 die from cardiovascular disease each year [65].

In 2012, it was estimated that among 37.9 million deaths worldwide, 46% were due to cardiovascular disease [65]. The regions with the highest rates of age-standardized cardiovascular disease mortality are in Central Asia, the Middle East, and Africa [65], while populous countries such as China and India have the largest absolute number of people dying from cardiovascular disease. In general, countries with lower rates of age-standardized cardiovascular disease mortality are more likely to have a high gross national income per capita, have high total health expenditure as a proportion of gross domestic product, and have non-communicable disease monitoring systems [65]. This suggests a beneficial impact of investment in healthcare and access to essential medicines despite the high prevalence of cardiovascular risk factors such as diabetes, obesity, and elevated cholesterol in these countries. Indeed, several studies in HIC suggest that the risk of cardiovascular disease in people with diabetes has been declining [66]. For example, in the USA, Australia, and Canada, a 46–53% relative reduction in cardiovascular mortality has been seen in people with diabetes since the mid-1990s, as well as a reduction in the excess mortality risk between populations with and without diabetes [66]. Despite this, people with diabetes are still two- to fourfold more likely to die from cardiovascular disease compared with people without diabetes [64].

Type 2 diabetes and cardiovascular disease have common precursors such as insulin resistance, visceral adiposity, and excess inflammation [67–71], as well as a complex mix of mechanistic processes including oxidative stress, enhanced atherogenicity of cholesterol particles, abnormal vascular reactivity, augmented haemostatic activation, and renal dysfunction [72]. Hence simply managing glucose, at least in the short term, has not been found to reduce cardiovascular events and mortality in large randomized controlled trials [73–75]. This has resulted in recommendations for individualized, comprehensive, multifactorial risk management (i.e. treating all risk factors together) for people with type 2 diabetes [65, 76, 77], adding to the burdens on individuals with diabetes, providers, and health systems.

Lower-extremity amputations

Lower-extremity amputations are a major complication for adults with diabetes owing to their physical, economic, and psychosocial burden. Amputation rates are an important indicator of the success of preventive care such as targeted glycaemic and cardiovascular risk factor management, and screening and treatment of people at high risk of foot complications. Peripheral artery disease and neuropathy are major risk factors for lower-extremity amputations. Population-based studies indicate that, in general, there have been variable reductions in amputation rates (by ~3–85%) since the early 1980s [66]. For the 13 countries or regions with available data (from Europe, USA, UK, and Australia), declines in amputation rates appear to be driven by declines in major lower-extremity amputations (i.e. amputations above the ankle), possibly as a consequence of more minor amputations being performed in order to prevent major amputations [66]. More recently, preliminary data in the

USA suggest that rates of lower-extremity amputations may be increasing, particularly among young adults with diabetes, though the underlying causes remain elusive. Regardless, lower-extremity amputation rates remain higher in people of other than white ethnicity and men, and large, geographical, within-country variations in amputation rates have been reported, with the suggestion that part of this relates to availability of high-quality footcare services [78–80].

Microvascular complications

Microvascular complications of diabetes include lower-extremity amputations, end-stage renal disease, retinopathy, and neuropathy. Duration of disease, age, and glycaemic and blood pressure management have all been found to be prominent modifying factors of microvascular disease onset, progression, and outcomes [81]. As for all data on diabetes-related complications, what we know of microvascular complications in diabetes stems from a relatively small number of studies from HIC. Here we highlight some of these.

End-stage renal disease

Together with hypertension, diabetes is the leading risk factor for nephropathy and end-stage renal disease requiring dialysis or transplant [82, 83]. In HIC, diabetes accounts for almost half of all new end-stage renal disease cases [82]. Like all other diabetes-related complications, the increase in diabetes prevalence has occurred simultaneously with steep increases (~40–700%) in end-stage renal disease incidence in the general population of several countries (e.g. USA, Australia, Russia, Korea, Mexico) [66, 84]. However, among populations with diabetes, the incidence of end-stage renal disease may be declining. For example, in a nationwide Chinese study, end-stage renal disease incidence declined 6% in adults with type 2 diabetes between 2000 and 2012 [85] and by 28% between 1990 and 2010 in the USA [86]. Similarly to amputation rates, recent US data suggest a stalling in progress of end-stage renal disease since 2010, and perhaps more concerning is an observed increase in end-stage renal disease in young adults (18–44 years) with diabetes [78]. A similar pattern of increasing incidence of end-stage renal disease among younger adults with type 2 diabetes has also been reported in Australia [87].

Retinopathy

Visual impairment, mainly due to cataract development, and retinopathy in diabetes are increasingly common, and diabetes is the leading cause of adult-onset blindness globally [81]. Diabetic retinopathy has devastating personal and socioeconomic consequences, despite being potentially preventable and treatable [88–90]. The overall prevalence of diabetic retinopathy and vision-threatening retinopathy in people with diabetes is estimated to be 35% and 12% [81], respectively. While considerable variation in diabetic retinopathy exists within and between countries, it is difficult to make meaningful comparisons in the absence of internationally agreed screening and diagnostic criteria for diabetic retinopathy. A 2019 review examined changes in retinopathy incidence over time and reported that despite the frequency of diabetic retinopathy, few population-based data existed. Of the few studies available (in USA, UK, and Korea), a 50–67% reduction in diabetic retinopathy since the 1990s was observed, most likely due to better glycaemic and blood pressure management, reductions in smoking, and earlier identification and treatment of diabetic retinopathy [66].

Neuropathy

Peripheral neuropathy is the most common form of diabetes-related neuropathy and occurs in 16–87% of people with diabetes [91], with severe and painful neuropathy occurring in approximately 26% of people [92]. Lower-extremity sensory loss and compromised peripheral vascular circulation increase the risk of ulceration and subsequent infection [93, 94]. The combination of neuropathy, infection, poor wound healing, and poor distal circulation increases the risk of lower-extremity amputation 15–20 times and is more common in LMIC (vs HIC) [1, 95–97]. Whether prevalence and incidence of neuropathy have changed over time is unknown due to the lack of data from repeated population surveys. In the USA, rates of hospitalization for neuropathy increased by 42.1% between 2000 and 2014 [98], though this is likely influenced by changes in International Classification of Disease (ICD) coding of neuropathy, as well as by increased awareness of neuropathy among individuals with diabetes and providers alike.

Acute complications

Acute complications of diabetes, such as diabetic ketoacidosis (DKA), the hyperglycaemic hyperosmolar state, lactic acidosis, and hypoglycaemia, most often require immediate medical management and can have fatal repercussions if left untreated. These acute complications of diabetes, despite being largely preventable, still account for a high proportion of the morbidity and mortality burden and contribute significantly to the high costs of diabetes care [99].

Aside from atypical variants such as ketosis-prone type 2 diabetes in Africans [13, 30], most acute metabolic complications occur in people with type 1 diabetes. In the USA, the SEARCH for Diabetes in Youth study reported that 29% of individuals aged <20 years with type 1 diabetes, and 10% with type 2 diabetes, presented with DKA at diagnosis [100]. The incidence of DKA in children and adolescents with type 1 diabetes also remains high, with ~1–12 episodes per 100 person-years [99].

When treated properly, the mortality from acute hyperglycaemic episodes such as DKA is extremely low (e.g. in Taiwan, the USA, and Denmark death occurred in 0.67–4.0% of all DKA cases) [101, 102]. In general, DKA-related complications have decreased among people with diabetes since the early 1990s [66], though recent increases in DKA and hyperglycaemic hyperosmolar state have been observed in the USA with underlying causes unknown [103]. Though data in LMIC by comparison are limited, in some African countries mortality from DKA can be as high as 25–33% [13, 104, 105]. This higher risk relative to HIC is likely due to a series of complex, cumulative, and interconnected barriers, such as poor access to healthcare, inadequate therapeutic instruments and medication, and insufficient numbers of trained staff, which result in poor metabolic management and subsequent higher risk of mortality [106]. Consequently, early-life death in people with type 1 diabetes in low-resource settings is commonplace (e.g. the post-diagnosis life expectancy in some regions of Africa is just one year) [107].

Mortality

Diabetes is associated with a 1.4–6-fold higher risk of mortality, depending on age, sex, and region [108] compared with the general population, and shortens life expectancy by up to 15 years [109].

In 2019, the IDF estimated that approximately 4.2 million adults aged 20–79 died as a result of diabetes and its complications [1]. This is equivalent to one death every eight seconds. Diabetes is estimated to contribute to 11.3% of deaths globally, ranging from 6.8% (lowest) in the Africa region to 16.2% (highest) in the Middle East and North Africa [108]. About half (46.2%) of the deaths attributable to diabetes occur in people under the age of 60 years, and this is as high as 73.1% in the Africa region and as low as 31.4% in Europe [108].

The most common causes of death among people with diabetes are cardiovascular disease, cancer, end-stage renal disease, and infections (e.g. pneumonia). Historically, in HIC, cardiovascular disease accounted for an overwhelming majority (i.e. 65–75%) of deaths in people with diabetes [110, 111]. However, as cardiovascular-specific mortality continues to decline [61–63], a larger proportion of deaths are being attributed to non-vascular causes such as cancer. For example, in the UK, the proportion of deaths due to vascular diseases in individuals with diabetes declined from 44% in 2001 to 24% in 2018, while the proportion of deaths due to cancer increased from 22% in 2001 to 28% in 2018 [63]. Similar findings have been shown in Australia and the USA [61, 112]. In low-resource settings, acute metabolic emergencies are still a prevailing cause of death in people with diabetes, accounting for 8%, 9.3%, and 11.9% of all deaths in populations in Mexico, India, and Asia, respectively [113–115]. End-stage renal disease also carries a high mortality, due mainly to the inaccessibility (physical and financial) of treatment (dialysis and/or transplant) in most LMIC settings [30, 113].

Mortality rates due to diabetes are often estimated from vital statistics systems (based on death certificate data), the accuracy of which may be affected by coding practices and country-level awareness of diabetes. This approach depends on the certifying doctor's opinion as to whether or not diabetes contributed to the death. Since this is subjective, mortality rates among populations with diabetes should ideally be estimated among defined cohorts with diagnosed diabetes. This approach captures all deaths among people with diabetes, and allows estimation of excess risk overall and for specific causes of death by comparison to the population without diabetes. Our current understanding of trends in all-cause mortality among people with diabetes comes from a relatively small number of HIC within North America, Europe, Australasia, and Asia. A recent systematic review, including 35 studies and representing 17 countries/regions from North America, Europe, Australia, Korea, and Taiwan, reported that since 2000 nearly 80% of studies reported declines in all-cause mortality among people with diabetes, and these declines occurred at a greater or similar rate to those without diabetes [60]. These declines were seen among people of predominantly European background.

More aggressive management of risk factors with statins, anti-platelet therapy, and anti-hypertensive medications [113, 116, 117], improvements in glycaemic management [116, 117], and smoking cessation [113, 116, 117] may have contributed to the substantial reductions in mortality rates. Because people with diabetes started with a higher mortality risk than those without diabetes, population-wide changes in risk factors [118–120] are likely to have led to a greater absolute risk reduction among people with diabetes than among those without. Though positive, falling mortality in people with diabetes will likely lead to an increasing prevalence of diabetes, despite a stable or even declining incidence of diabetes. This will increase the total years of life spent living with diabetes and may drive the emergence of *new* diabetes-related complications that previously did not substantially contribute to the diabetes burden.

Emerging complications

The longer life expectancy among people with diabetes and fuller assessment of the overall impact of diabetes have driven the recognition of non-traditional complications of diabetes, including cancer, mental health disorders, and physical and cognitive disability [68]. There has also been an increasing interest in the impact of diabetes on infection risk. Here, we provide a high-level overview of the existing evidence describing these associations.

Cancer

A large body of epidemiological evidence now suggests that people with diabetes are at an increased risk for cancer, though the magnitude and direction of the association depend on the specific site of the cancer [121]. The strongest associations have been demonstrated for liver [122] and pancreatic [123] cancers, though these may also reflect some degree of reverse causality, with the cancer itself leading to the onset of type 2 diabetes. Risk of endometrial cancer [124] appears to be doubled in women with diabetes, and risks of breast [125], colorectal [126], bladder [127], stomach [128], kidney [129], and non-Hodgkin's lymphoma [130] are approximately 20–40% higher in people with type 2 diabetes. Interestingly, there appears to be a protective effect of diabetes for prostate cancer of ~10–15% [131], which is thought to be due in part to reduced levels of endogenous testosterone in men with type 2 diabetes. A 2015 Australian study, using a large national diabetes registry and including more than 1 million people, also demonstrated increased risks for gallbladder, lung, ovarian, and thyroid cancers, multiple myeloma, and leukaemia [132]. Many of these cancers are also associated with obesity [133] and this may be a key driver for the increased cancer risk in people with diabetes.

The majority of current evidence pertains to type 2 diabetes, though some studies show similar risks for type 1 diabetes [132, 134], suggesting the underlying causal mechanism may be hyperglycaemia, rather than hyperinsulinemia, though clinical trials are yet to demonstrate a causal association between reduced glucose levels and reduced cancer risk [135]. Studies examining anti-diabetes drugs, including insulin and metformin, have also shown some associations with cancer risk, though such studies are difficult to interpret as they are prone to bias due to confounding by indication.

Once diagnosed with cancer, people with diabetes are at increased risk for mortality. The same Australian study that examined cancer incidence in over 1 million people with diabetes demonstrated increased risks for overall cancer mortality and a number of site-specific cancers, similar to results for cancer incidence [132]. However, prospective studies on site-specific cancer mortality are extremely difficult to conduct owing to the relative rareness of cancer (and diabetes) and the need for very large sample sizes to conduct such studies. Smaller studies have also demonstrated that among those diagnosed with cancer, diabetes confers a 30% increased risk for all-cause mortality. The proportional shift of increasing cancer deaths in people with diabetes over time [61, 63, 112] suggests screening for several cancers should be prioritized in people with diabetes to minimize cancer-related mortality in the future.

Mental health disorders

People with diabetes are at increased risk for major depressive disorder [136], anxiety [137], eating disorders (particularly in female adolescents with type 1 diabetes) [138], and serious mental illness

(e.g. schizophrenia) [139]. Further, diabetes has been found to be a significant risk factor for suicidal ideation [140–142], hopelessness, and poor quality of life in adults [143]. These mental health issues interfere with optimal self-management and may lead to other diabetes complications and increased risk for all-cause mortality [144, 145].

Cognitive impairment

With an ageing population, dementia has become one of the most common conditions in modern society with devastating personal, societal, and economic consequences. Several meta-analyses have demonstrated an adverse effect of diabetes on cognition, with increased risks ranging from 21% to 91% depending on the impairment being measured [146–148]. A 2019 updated meta-analysis, representing 122 studies and over 9 million individuals from Western populations, found that diabetes was associated with a 49%, 43%, 43%, and 91% increased risk of mild cognitive impairment, all-cause dementia, Alzheimer's disease, and vascular dementia, respectively [149]. This same study also reported a non-linear *dose response* such that the risk of cognitive disorders increased by 20% with fasting plasma glucose above 7.75 mmol/l [149]. Diabetes has been associated with more specific cognitive impairments such as decrements in episodic memory, logical memory, executive functions (e.g. cognitive flexibility), and speed of processing, but not short-term or working memory [147]. Encouragingly, some evidence indicates that diabetes drugs may reduce the risk of dementia in people with diabetes. Pioglitazone, for example, an oral anti-diabetes drug, has been associated with a 47% reduction in dementia risk [149].

Disability

Diabetes can lead to disability in various ways. Excluding the medical aspects of diabetes-related complications that directly restrict bodily function, diabetes may be considered a *hidden* disability, whereby the individual concerned is hampered from partaking in routine activities but displays no physical manifestation of this illness. For example, children with type 1 diabetes may suffer discrimination at school or may not be permitted to engage in physical activities [150]. Adults in the workplace may suffer lower work performance by virtue of any number of symptoms (impaired fine motor skills and concentration, grogginess, urinary frequency) [151], or even a decline in cognitive functioning [152–154]. People with diabetes take more working days off and often report difficulties with completing work tasks [155, 156]. The physical manifestations of diabetes become more significant with the development of complications. Visual impairment, restricted mobility (due to shortness of breath, chest pain, or even amputation), and general ill-health (ranging from increased susceptibility to infection to uraemia related to irreversible renal dysfunction) may all contribute to physical disability [151, 157]. In a 2013 meta-analysis of 26 studies, Wong et al. demonstrated that diabetes (vs no diabetes) was associated with a 70% increased risk of mobility disability, a 65% increased risk for limitations in instrumental activities of daily living (e.g. shopping, using transport), and an 82% increased risk for limitations in activities of daily living (e.g. bathing, dressing, eating, using the toilet) [158]. A Global Burden of Disease study subsequently reported that in 2016, lower-extremity complications of diabetes (i.e. diabetic neuropathy, foot ulcer, and amputation) contributed 16.8 million years lived with disability (YLDs), or 2.1% of the global (YLDs) [159], an increase of 140.3% since 1990. This disability burden disproportionally affects men and those aged 50–69 years. By region, the highest YLD rates were seen in North Africa and the Middle East, Latin America, Oceania, and the Caribbean, while the lowest rates were in East Asia, Western sub-Saharan African, Australasia, and Western Europe [159]. Diabetes management strategies, including interdisciplinary foot-care services, are necessary to reduce the disability burden through the prevention of diabetes-related complications.

Infections

Individuals with diabetes have an increased risk for tuberculosis, severe Gram-positive infections, hospital-acquired postoperative infections, urinary tract infections, and tropical diseases compared with people without diabetes [160]. This increased risk is of particular concern in LMIC, where the relative burden of these communicable diseases remains high [161]. This challenge is not just one of parallel epidemics, as diabetes predisposes both to higher risk of infections [162] and possibly poorer outcomes for those who contract infections. Data from observational studies increasingly show that tuberculosis disease severity (e.g. sputum smear grade [163, 164], haemoptysis, cavitation [163, 165–167], and drug resistance [167]), treatment failure, tuberculosis relapse, and death appear greater among those with tuberculosis and diabetes than those with tuberculosis alone. According to 2012 American Diabetes Association data, ~25% of all inpatient hospital stays are incurred by people with diabetes [168]. In a 2019 US study, infection-related hospitalizations were almost four times as high in adults with versus without diabetes, and as much as 15.7 times as high for some infection types [169]. Concerningly, between 2000 and 2015, increasing rates of sepsis, influenza, kidney infections, osteomyelitis, and cellulitis were observed in people with diabetes, and rates of pneumonia, foot infections, and mycoses declined in adults without, but not with, diabetes [169], highlighting the need for greater infectious risk mitigation in adults with diabetes, even in HIC. Covid-19 does not appear to be substantially more frequent in people with diabetes, but a large UK study reported that mortality risks for Covid-19 were doubled in type 2 diabetes and trebled for type 1 diabetes [170].

Economic costs of diabetes

Diabetes is an economically costly disease. In 2019, the global direct health expenditure of diabetes was estimated to be US $760 billion, with the highest spending in the USA ($294.6 billion), China ($109.0 billion), and Brazil ($52.3 billion). This spending is expected to grow substantially, with estimates projecting expenditures of $825 billion by 2030 [171]. Also by 2030, 90% of the global expenditure for diabetes will be in the world's richest countries [172, 173], even though the majority of individuals with diabetes live in LMIC [1]. This exemplifies Julian Tudor Hart's [174] *inverse care law*, where 'the availability of good medical care tends to vary inversely with the need for it in the population served'.

Though staggering, these costs likely underestimate the true economic toll of diabetes, as associated cardiometabolic conditions, secondary complications of diabetes, and costs among people with undiagnosed diabetes are not included in overall estimates [175]. Persistent hyperglycaemia results in ~30% higher annual pharmaceutical costs, 70% higher laboratory and diagnostic costs, and 85% higher consultation costs compared with

well-managed diabetes [176]. Roughly, for every 1 percentage point (11 mmol/mol) increase in HbA_{1c} over 7% (53 mmol/mol), there is a 10% increase in related costs [177]. Given that the prevalence of undiagnosed diabetes is high globally, particularly in low-income countries (LIC), the true cost of diabetes remains underestimated [1, 53]. Finally, total diabetes costs should reflect costs associated with recommended lifestyle adaptations. For instance, the two-year cost of walking three miles daily is up to $400, calculated by including the cost of time, exercise apparel and shoes, transportation, and gym memberships [178], and dietary modification costs make up 20% of the direct ambulatory care costs for people with diabetes [179].

For a chronic condition requiring long-term medical care, management plans of varying complexity, and screening and management of secondary complications, diabetes costs are multifactorial and complex. The total cost of diabetes reflects direct costs (costs of treatment and care including outpatient consultations, inpatient care, screening and diagnostic testing, therapeutic procedures, medications, and paramedical care as well as associated costs such as transport to appointments), indirect costs (lost economic productivity due to disability, morbidity or mortality due to diabetes), and intangible costs (costs associated with psychosocial impacts or altered quality of life).

Diabetes costs vary by both clinical and demographic characteristics. Although type 1 diabetes accounts for a relatively small proportion of the total cost of diabetes, the per capita cost is almost twice that of type 2 diabetes [180], likely driven by the need for more frequent consultations, universal use of insulin, and faster progression to retinopathy and nephropathy compared with type 2 diabetes [51, 181]. Among individuals with type 2 diabetes, coexisting hypertension and dyslipidaemia are a more significant component of total costs [175, 177]. Per capita diabetes-related costs are also higher for men than for women and among older age groups [182, 183].

Between-county comparisons of total diabetes costs are challenging. The approaches used to estimate economic costs of disease vary in terms of perspective taken (e.g. individual, society), methodology used, data sources, and year of estimation. Country-wide or region-wide costs are reliant on diabetes incidence and prevalence data, which may be uncertain, incomplete, or based on unstandardized data. Furthermore, different settings can vary widely in purchasing power and clinical patterns. For example, auxiliary services such as dieticians or home nursing are more likely to contribute to costs in HIC settings where these services are more widely available and used. Similarly, medication costs vary across settings due to drug costs and availability, and use of medications among those with diagnosed diabetes is markedly lower in LIC compared to HIC (29.6% vs 74.0%) [184].

Broadly, healthcare expenditure among those with diabetes is ~2–5.6-fold times that of the general population [168, 182, 185–187], although the patterns of spending and costs vary across settings. In HIC, these costs are largely driven by the high costs of complications and associated hospital care, while costs in LIC are largely driven by medication costs [175, 188, 189]. Medication spending accounts for 32–60% of total diabetes expenditures in countries such as Mexico, India, Pakistan, and Sudan [188]. The difference in country-level diabetes expenditure and total diabetes costs trickles down to households and individuals. In industrialized countries, availability of public or private insurance and financing of the healthcare system bears some or all of the cost of diabetes care, while in LMIC this cost is largely born by the household. Out-of-pocket spending for diabetes ranges from 40% to 60% in LMIC [30, 107, 190, 191], and in LIC the cost of insulin can be as high as 65% of the total household income [184]. These costs can be catastrophic for the poorest individuals, with the lowest income groups paying the largest portion of their household income towards diabetes care [191, 192]. This added expense can lead to further poverty, less ability to access necessary care and medications, and further increasing risk of life-threatening complications [189]. On a national level, the economic impact of this is also greater in LMIC, where the burden of diabetes is highest among the individuals in the most economically productive age range (15–59 years) [193]. A higher burden among the working-age population can slow the economic development of transitioning countries, further decreasing the ability of these countries to slow disease progression [2]. The resulting spiral of disease and poverty exacerbates already marked disparities between HIC and LIC.

Socioeconomic costs of diabetes

In addition to medical or biological dysfunction, diabetes may impair a person's ability to perform domestic and occupational activities and restrict them from fully integrating into society. For example, those requiring insulin may be limited by highly structured activities of daily living (glucose monitoring, insulin administration, timed eating), recurrent hospitalizations, hyper- and hypoglycaemic episodes, and regular preventive or therapeutic medical visits. This is likely to be exacerbated in LMIC where access to insulin pumps, continuous glucose monitoring, and other technologies are not available. In the DAWN2 study, ~40% of participants reported that their medication interfered with their ability to live a normal life, and 57% reported that they were not working because of their disease [194]. Mental health burdens, such as depression, can also have a significant impact on workplace absence and/or poor productivity [195].

Given a large number of people with diabetes are of working age, particularly in LMIC, understanding the impact of diabetes on workforce productivity is of growing interest for employers and governments alike. Productivity loss in the workplace occurs because of absenteeism (absence from work due to illness) as well as presenteeism (reduced efficiency while at work) [196]. In the USA, as much as $58 billion annually is lost to diabetes as a result of loss of earnings owing to unemployment, reduced work efficiency, permanent disability, and death [168]. For LIC, the impact of diabetes on workplace productivity is expected to be proportionally larger as premature deaths are more common, including among those of economically productive age [1].

One measure that is being increasingly used to describe the socioeconomic impact of diabetes is productivity-adjusted life years (PALYs), a novel measure developed to adjust the years of life lived for productivity loss attributable to diabetes, similar to the measure of quality-adjusted life years (QALYs) that adjusts for a reduction in quality of life [197]. For example, in Australia, diabetes reduces PALYs by 11.1%, equivalent to 1.4 PALYs lost per person, with the greatest impact on the youngest adults [197]. In Germany, mean PALYs lost per person with type 2 diabetes in 2020 were 2.6 years, with younger age groups and women expected to lose more PALYs compared with older age groups and men. Though this metric, to date, has not been reported broadly by many

countries, it represents a useful measure, in addition to QALYs, of the economic impact of diabetes on the broader society.

In addition to the workplace, diabetes can have a negative impact on individuals' interpersonal relationships. In the DAWN2 study, 20% of surveyed participants reported that diabetes had had negative impacts on their family and peer relations [194]. Some studies have also shown that people with diabetes have low levels of social integration (e.g. low contact with family) and support (e.g. living without a partner) [198, 199]. Strong social networks and good social support are associated with fewer psychosocial problems and better self-management among people with diabetes and should be considered as part of a multifaceted approach to diabetes care [195, 200].

One in five people with diabetes and their families experience some form of discrimination [194, 201]. The reasons for discrimination are varied; one involves perceiving that people with diabetes are using up societal resources [202]. As a result, stigma is common among people with diabetes and prevents them from disclosing their disease. For instance, adolescents with type 2 diabetes have reported hiding their diagnosis from their peers because they fear their reaction [203], and adults with diabetes have reported that disclosing their disease to their supervisors and colleagues would jeopardize their job [202] or, possibly, their educational opportunities or marital prospects [204, 205]. Owing to the stigma attached to type 1 diabetes, some parents choose not to disclose the condition of their child to relatives [205]. Use of insulin adds to the stigma, as people with diabetes report feeling mistaken for intravenous drug users [202, 203]. Societal stigma and discrimination are significant barriers to self-management and to improving care and social support for individuals with diabetes.

The individual and societal dysfunction associated with disability is difficult to quantify. Several methods have been used in attempts to quantify diabetes-related disability, but most suffer from at least some imperfection owing to the necessity for making judgements about the value of activities and subjectivity of responses. This is especially difficult where there are cultural and ideological dissimilarities between the evaluator and the population being appraised.

Gaps and future directions

Diabetes imposes serious health, social, and economic burdens worldwide. However, we still need more widespread and reliable data regarding burdens, access, and expenditures, especially in LMIC where the greatest burdens of diabetes occur. Few longitudinal studies are available in LMIC, thus limiting our understanding of incidence, risk factors, pathophysiology, variations in phenotypes, and natural history in these settings. In addition, studies are needed that include both long-understood and emerging complications of diabetes, such as cognitive function, to create better estimates of diabetes-attributable mortality, morbidity, and cost. Assessing burdens using reliable, consistent methods will aid our comprehension of the complex mix of programmed, predisposing, and modifiable factors associated with diabetes and lay a foundation for policy development and advocacy.

Despite varied estimates, the pattern is consistent: people with diabetes experience more symptoms, morbidity, comorbidities, and higher mortality rates than those without diabetes. They suffer diminished functional capacity and more psychosocial illness, and they incur greater costs for healthcare, self-care, and losses in earning potential and societal roles. Needless to say, intervening before diabetes onset may hold great benefit in reducing global burdens. However, although there is evidence from large trials demonstrating that prevention can forestall conversion from pre-diabetes to diabetes [206–209], widespread translation of these findings is hampered by multi-level barriers (political, social, cultural, behavioural, and economic factors). Preparation for the increasing diabetes burden requires progress in the wider collection of reliable data, collected in a standardized manner across various countries (especially assuaging the scarcity from LMIC regarding diabetes-related mortality, complications, disability, and costs), and a greater emphasis on cost-effectiveness studies that may inform better resource allocation [210]. On the shoulders of compelling evidence, greater investment and political will are required to overcome low accessibility and awareness, and also to translate the evidence into the practical, real-life implementation of proven and effective prevention strategies.

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A L G r a w a n y

4 Epidemiology of Type 1 Diabetes

Lars C. Stene[1,2] and Jaakko Tuomilehto[3,4,5]

[1] Department of Chronic Diseases, Norwegian Institute of Public Health, Oslo, Norway
[2] Oslo Diabetes Research Centre, Oslo University Hospital, Oslo, Norway
[3] Department of Public Health, University of Helsinki, Helsinki, Finland
[4] National School of Public Health, Madrid, Spain
[5] Diabetes Research Group, King Abdulaziz University, Jeddah, Saudi Arabia

Key points

- Type 1 diabetes develops in genetically susceptible individuals after a pre-clinical phase of variable length, usually with immune-mediated destruction of pancreatic β cells, and requires lifelong treatment with insulin.
- Type 1 diabetes can occur at any age, but the incidence peaks around puberty. Distinguishing between type 1 diabetes and type 2 diabetes becomes increasingly difficult with age in adults.
- In childhood, the incidence is not much different in girls and boys, but especially in high-incidence populations there is usually a male excess. There is a 1.3–2.0-fold male excess in incidence after the age of ~15 years in most populations.
- The incidence in childhood varies enormously between countries. Some Asian and American native populations have low incidences (<5 per 100 000 population per year), while Finland has the highest incidence, at around 60 per 100 000 population per year in 2006. Kuwait, Sweden, and Norway also have high incidences (>35 per 100 000 population per year). North America and Australia have moderate to high incidences, while eastern European countries have low to moderate incidences. Most European countries have incidences that have recently risen to 20 per 100 000 population per year.
- About 10–20% of children with newly diagnosed type 1 diabetes have an affected first-degree relative. Those with an affected sibling or parent have a cumulative risk of 3–7% up to about 20 years of age, compared with a cumulative risk of 0.2–0.8% in the general populations. The cumulative incidence among the monozygotic co-twins of individuals with type 1 diabetes is less than 50%, even after >30 years of follow-up.
- Some of the geographical differences and familial aggregation may be explained by human leucocyte antigen (HLA) haplotypes.
- The incidence of childhood-onset type 1 diabetes has increased by 3–4% per calendar year, and there has been a tendency towards younger average age at onset over time. Finland and a few other countries seem to have experienced a plateau or decrease in incidence among children since 2005, but whether this is due to random variation need to be confirmed. The causes of the changing trends are unknown.
- Virus infections and nutritional factors have been implicated, but no specific environmental risk factor has been established.
- Even though insulin replacement therapy and other advances in the management of type 1 diabetes have improved the prognosis of people with type 1 diabetes, their mortality is still at least two times (~two- to eight-fold) higher than in the background population in high-income countries. This is because of both acute and chronic diabetes-related complications, including cardiovascular disease from the age of ~30 years. In low- and middle-income countries mortality in type 1 diabetes remains very high.

Type 1 diabetes in most cases results from an immune-mediated destruction of the pancreatic β cells due to an unknown cause leading to a lifelong requirement for insulin treatment. This occurs after a pre-clinical period of varying length when autoantibodies to insulin, glutamine acid decarboxylase (GAD), insulinoma-associated antigen 2 (IA-2), and other islet autoantigens can be detected [1]. These autoantibodies are markers of ongoing β-cell destruction, but are not thought to be pathogenic. Persistent positivity for two or more islet autoantibodies in early life is associated with a high probability of developing type 1 diabetes in genetically susceptible individuals – approximately half of such people develop type 1 diabetes within 5–7 years [2, 3].

Genetic factors influence the susceptibility to type 1 diabetes, particularly HLA genes (Chapter 12) [4, 5]. The combination of HLA class II haplotypes DR3-DQ2 and DR4-DQ8 confers a very high risk of type 1 diabetes, while those who carry only one of the two risk haplotypes have a moderately increased risk. Several other HLA alleles, including those in class I loci, further influence the genetic risk. More details on the role of genetic factors and the pathological process are covered in Chapter 14. Diagnosis of type 1 diabetes among children is usually relatively simple, typically with severe symptoms and marked hyperglycaemia, but classification and early detection of type 1 diabetes become increasingly difficult with increasing age.

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Occurrence of type 1 diabetes by age, sex, place, and time

The World Health Organization (WHO) DIAMOND Study (Multinational Project for Childhood Diabetes) [6] and the EURODIAB ACE Study [7] have collected standardized incidence data for type 1 diabetes among children aged under 15 years, based on notification by the diagnosing physician and date of diagnosis, defined as the date of first insulin injection. In both projects, the degree of undercounting of cases has been estimated using a second source of information. Later, additional population-based incidence studies have been published from various countries [8].

Incidence rates are calculated as the number of new cases per 100 000 person-years. Person-years are typically estimated by the mean population size in each calendar year, sex, and age group. The proportion of the population expected to develop the disease by a certain age – that is, the cumulative incidence – can be approximated by multiplying the average incidence rate in an age group by the number of years covered by the age group. For instance, if the average incidence rate among 0–14-year-olds is 20 per 100 000 person-years, then approximately ([20 per 100 000] × 15 = 0.003 =) 0.3% of children will develop disease before 15 years of age. Note that this corresponds closely to the prevalence at age 15 years (not accounting for mortality), while the prevalence in the age group 0–14 years will be substantially lower.

Most of the currently available incidence data come from studies of European children. Incidence data from Africa are still sparse, but increased information about the incidence of type 1 diabetes among Asian and South American populations has changed the understanding of the global patterns of variation in incidence [8].

Occurrence of type 1 diabetes by age

Type 1 diabetes may occur at any age and the incidence rate varies by age (Figure 4.1). Type 1 diabetes is not present at birth and is rare in the first two years of life. Onset of type 1 diabetes before 12 months, and even before 6 months, may occur in rare instances, but monogenic or syndromic forms should be suspected, as these represent a sizeable proportion of cases with diabetes diagnosed in this age group [11].

The incidence rate increases from age 6 months to peak at around 9–14 years, a common finding over time and across populations with different incidence rates [6, 9, 10, 12–16]. The incidence among 15–29-year-olds is lower than among 0–14-year-olds in most studied populations. In some populations there appears to be an additional rise in incidence after the age of ~25–30 years [17–19].

There are few population-based incidence studies for older age groups above 35 years of age and especially few covering the whole age range [16]. For many years, the only two sources of the latter were Minnesota, 1945–1969 [20], and a nationwide study from Denmark, 1973–1977 [21]. More recent data have been published from China 2010–2013 in a nationally representative sample of approximately 10% of the population [10] (Figure 4.1b) and Olmsted county, Minnesota [22]. In the Olmsted county study between 1994 and 2010, approximately half of the 233 individuals with incident type 1 diabetes developed the condition below 15 years of age, 25% between 15 and 30 years, and 25% after 30 years of age [22]. The corresponding proportions among the over 5000 individuals with incident type 1 diabetes in the Chinese study were 25% below 15 years, 33% among 15–29-year-olds, and nearly 40% after 30 years of age [10].

It may be difficult to distinguish type 1 diabetes from type 2 diabetes in some adults, especially after ~30 years of age. In the Swedish nationwide prospective incidence study of 15–34-year-olds, 78% of the newly diagnosed individuals were classified as having type 1 diabetes and 15% as having type 2 diabetes at the time of the diagnosis [23]. The follow-up showed that 92% of the individuals diagnosed before 30 years of age were treated with insulin later [24]. These findings are consistent with incidence data from Finland among people aged 15–39 years [25, 26]. In these studies, the incidence of type 2 diabetes exceeded that of type 1 diabetes after the age of ~30 years. By contrast, in Turin, Italy, which has a much lower incidence of type 1 diabetes, the incidence of type 2 diabetes is about three times higher than that of type 1 diabetes at the age of 30 years [17]. Although beyond the scope of this chapter, it is important to consider the possible clinical heterogeneity and increasing difficulty of classification of diabetes with increasing age. Some of the apparent heterogeneity may represent extremes along a continuum [27].

Incidence by sex

The peak in incidence rate among children occurs slightly earlier in girls than in boys (Figure 4.1a), suggesting an influence of puberty [9, 12, 22]. During the 1970s there was a male excess of type 1 diabetes in children in populations of European origin and a female excess in populations of African and Asian origin [28]; however, during the early 1990s the sex-specific pattern in incidence among children changed towards more modest differences. Only 6 of 112 centres with data during 1990–1999 showed a significant excess among females (Beijing, Hong Kong, and Zunyi in China; New South Wales in Australia; Puerto Rico and the Afro-American ethnic group in the USA), while 6 centres showed a significant male excess (West Bulgaria, Finland, Attica in Greece, Switzerland, Oxford in the UK, and the Dominican Republic), and all differences were generally of modest magnitude [6].

In young adults, there is a male excess in the majority of studied populations [16]. While the male-to-female ratio among children in most populations is 0.9–1.1 [6], the ratio among young adults ranges from about 1.3 up to 2.0 in many populations [15, 16, 29]. In the study of incident cases across all ages in China, the male-to-female ratio was 0.90 under the age of 15, but 1.35 after 15 years of age, directionally consistent with that seen in high-incidence countries [10].

Incidence by country

The incidence of type 1 diabetes among children shows a vast geographical variation worldwide, with high rates in the Nordic countries and Kuwait, and low in South-East Asia and parts of South America (Figure 4.2). During 1990–1999, the age-adjusted incidence rate of type 1 diabetes ranged globally from 0.1 in Zunyi (China) and Caracas (Venezuela) to 37.8 in Sardinia and 40.9 per 100 000 per year in Finland [6]. More recently, the highest recorded incidence of childhood-onset type 1 diabetes was ~60 per 100 000 in 2006 in Finland [30, 31].

Many European countries have robust type 1 diabetes registries, which demonstrate an approximately 10-fold difference between the highest- and lowest-incidence countries in Europe around the turn of the millennium [32]. A six- to eightfold difference within Europe has later been recorded after increasing incidence, with a majority of European countries showing rates of 20 per 100 000 per year or higher during 2008–2013 [7]. In general, the incidence is lower in eastern European than western and northern European countries.

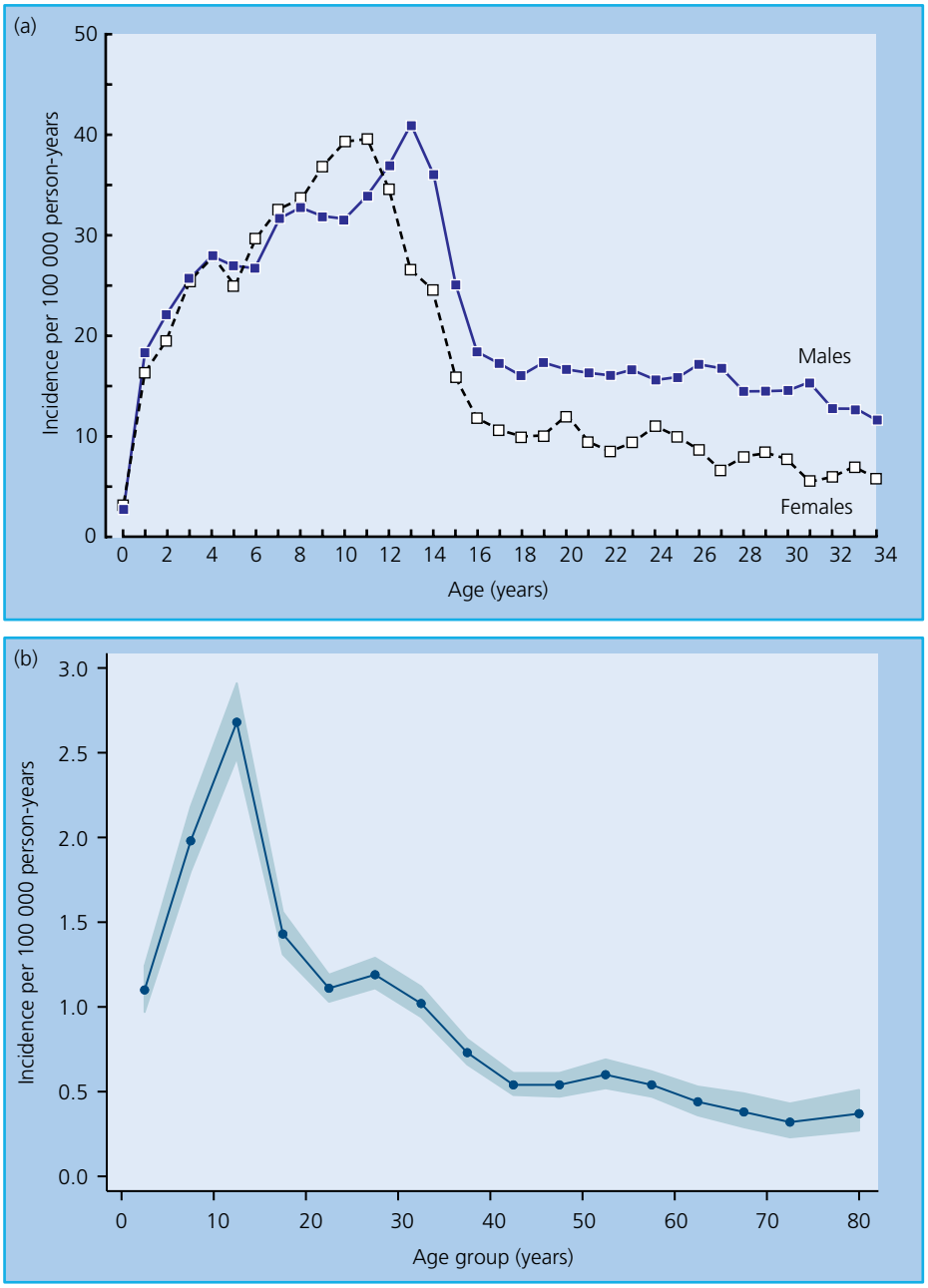

Figure 4.1 Incidence of type 1 diabetes by age and sex. (a) Incidence in Sweden by age and sex during 1983–1998. Source: Reproduced from Pundziute-Lyckå et al. 2002 [9], with permission from Springer-Verlag. (b) Incidence of type 1 diabetes by age group in China during 2010–2013. The upper age group was ≥75 years, placed at 80 years on the x-axis. Shaded area represents pointwise 95% confidence intervals. Source: Produced with data from Weng et al. 2018 [10].

Data in people aged 15–29 years in European centres (in Belgium, Lithuania, Romania, Sardinia, Slovakia, Spain, Sweden, and the UK) showed incidence rates between 5 and 12 per 100 000 per year during 1996–1997 [15]. Incidence rates among 15–29-year-olds within this range have also been reported, albeit from earlier time periods, in other European centres, such as 5.5 per 100 000 year in Rzeszow, Poland, 1980–1992 [33]; ~7 per 100 000 per year in Turin, mainland Italy 1984–1991 [17, 34]; and ~13 per 100 000 per year in two regions of Denmark, 1970–1976 [35]. While Sweden and Sardinia have higher incidence rates among children, the incidence rate among young adults was not much higher in Sardinia and Sweden than in the other centres in the multicentre study [15]. Older data from Norway (1978–1982) [14] indicated a higher incidence rate of 17 per 100 000 per year and more recent data from Finland (1992–2001) [25] reported an incidence rate of 18 per 100 000 per year among 15–29-year-olds. Recent data on new users of insulin (and no other anti-diabetes drugs) indicated stable incidences over 30 per 100 000 per year among individuals aged 5–29 years in Norway during 2006–2010 [36]. In addition to problems with correct classification of type of diabetes in adults, incomplete ascertainment may also be a greater problem for young adults than among children [37], while incomplete ascertainment is not a likely problem with the insulin use data. Differences between countries in the incidence among young adults should be interpreted with caution until more data are collected using comparable methodology.

The USA is represented in the DIAMOND project with the data collected during the 1990s from Allegheny County in Pennsylvania,

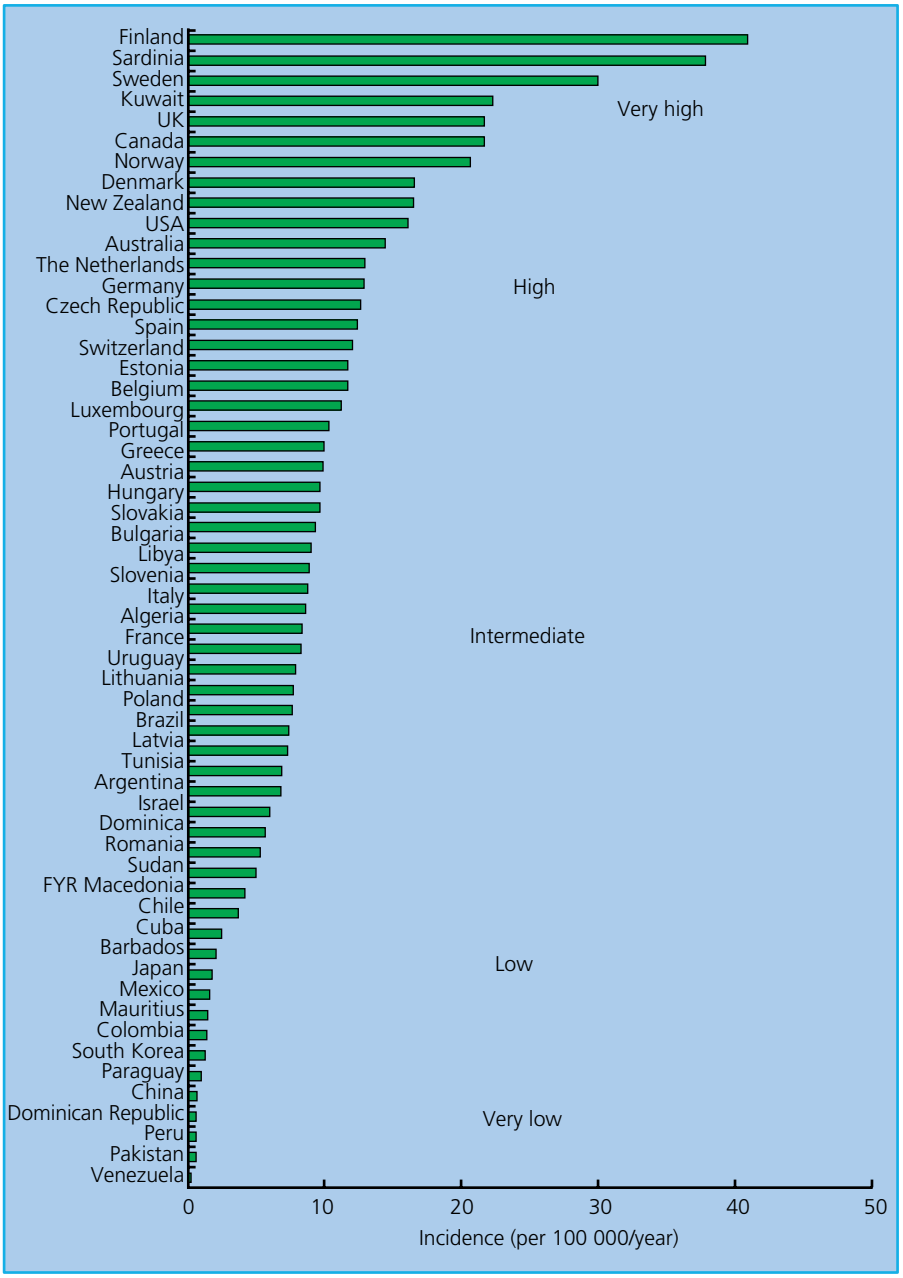

Figure 4.2 Geographical variation in childhood-onset type 1 diabetes incidence rates, 1990–1999. Most registries were not nationwide and several countries display within-country variation. Source: Reproduced from the DIAMOND Project Group 2006 [6] with permission from John Wiley & Sons Ltd, Chichester.

Chicago, and Jefferson County in Alabama, with incidence rates in the range 11–18 per 100 000 per year among children. Newer data from the USA from around 2000–2017 have suggested an incidence of ~20 per 100 000 per year [38–40]. Alberta and Calgary in Canada had slightly higher rates (~23 per 100 000 per year; Figure 4.2) [6], while the data from the Avalon Peninsula, Newfoundland, indicated a higher incidence rate of 35.9 per 100 000 per year [41].

In South America, children in centres in Venezuela, Paraguay, and Colombia had incidence rates of less than 1 per 100 000 per year; Chile (Santiago) had ~4 per 100 000 per year; while Argentina and Brazil had an average of ~8 per 100 000 per year. Data from Argentina and Brazil came from populations with a low proportion of Indigenous Indian populations, whereas the other countries had a significant proportion of Indigenous people. Many centres in Central America and the West Indies (except Puerto Rico and St Thomas's) generally have low to intermediate incidence rates [6].

Data from New Zealand and parts of Australia show moderate to high incidence rates (15–25 per 100 000 per year) among children [6]. Data from other Pacific Island countries are lacking and would be difficult to interpret because the populations in most island countries are small. In Asia, the mean incidence rate among the 23 centres in China during the early 1990s was 0.8 per 100 000 per year. In a recent study in China, the incidence varied between 1.2 and 3.6 [10]. Kuwait had a dramatic increase in incidence from 17.7 in 1992–1994 to a rate of 40.9 per 100 000 per year in 2011–2013 [42].

There is limited information on the incidence rate of type 1 diabetes from sub-Saharan Africa [43]. The five DIAMOND centres

were in North Africa (Algeria, Libya, Sudan, and Tunisia) and Mauritius. Incidence rates reported from these centres ranged from low to intermediate, but these countries cannot be said to be representative of all of Africa. Additional incidence data from other regions are discussed in later sections.

Trends in incidence over time

Most countries have experienced an increasing incidence of type 1 diabetes among children over recent decades, with differences in time trends between countries and calendar periods (Figure 4.3).

The methodology for population-based incidence registries was not standardized until the late 1980s, but several older data sources have been reviewed to assess possible time trends. There is a general impression that the incidence of type 1 diabetes increased markedly after the middle of the twentieth century [55, 56], although in Denmark the incidence among 0–29-year-olds seemed stable from 1924 to the 1970s [35]. An analysis of incidence trends of more standardized registry data from 1960 to 1996 in 37 populations worldwide showed a significant increase in incidence rates over time in the majority of populations, with a steeper relative increase in low-incidence than in high-incidence populations [57].

In the 103 centres participating in the WHO DIAMOND project for at least three years during 1990–1999, the overall relative increase in incidence rate was 2.8% per year [6]. By continent, overall increasing trends per year were estimated at 5.3% in North America, 3.2% in Europe, and 4.0% in Asia [6]. The only region with an overall decreasing trend was Central America and the West Indies [6].

In general, the increasing trend appeared to be most marked in the centres with high and very high incidence rates during the 1990s. In the centres with low and very low incidence rates, there were no significant increases in incidence rates over time. However, the time trends in Europe reported to EURODIAB for 1989–2013 indicated an overall mean increase in incidence rate of 3.4% per year, with a tendency towards bigger relative increases in the countries with the lowest average incidence rates during the initial years of registration [7].

A smaller relative increase in incidence rate over time among older individuals than among younger ones has been seen in some European studies covering wider age ranges [9, 18, 19, 58, 59]. This latter observation is in line with a model where a certain pool of genetically susceptible individuals develop diabetes at younger ages [9, 18, 60]. The few available data, however, are not entirely consistent with this idea. An increasing incidence rate has also been seen among older age groups in some populations [19, 26, 34], but the lack of standardized incidence data covering the whole age range makes it difficult to draw firm conclusions. Despite the time trends indicated in Sweden with decreasing average age of onset, the peak incidence rate remained around the age of puberty [9].

While a greater relative increase over time among 0–4-year-olds than among 10–14-year-olds was seen in European children during 1990–1999 in the DIAMOND project, this was not seen in Asia and North America [6]. More recent data from Europe show that the relative increase over time has been similar across age groups in the long run [7]. The recent declining incidence in Finland and Australia (discussed shortly) was seen for 0–14-year-olds overall, but was most marked among children aged 0–4 years [31, 61].

In Finland, the incidence rate increased linearly from the mid-1960s to the mid-1990s [44] and thereafter even more steeply,

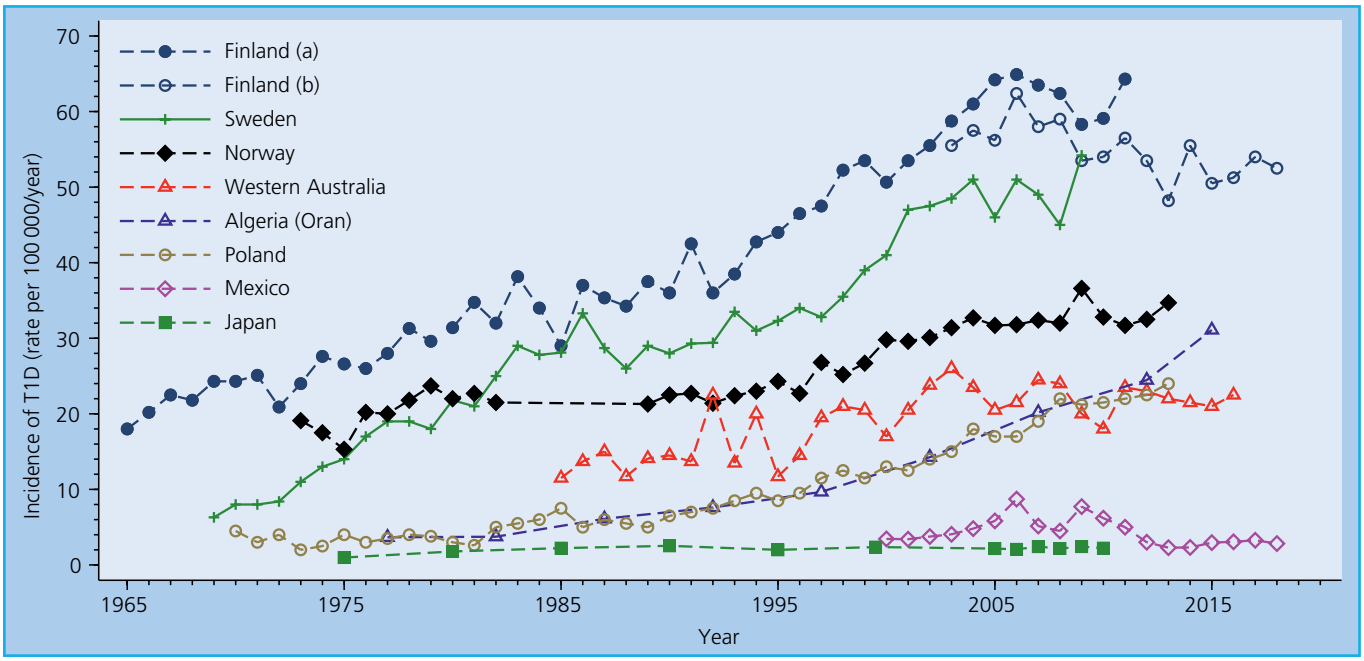

Figure 4.3 Long-term time trends in incidence rate of type 1 diabetes (T1D) in children in selected countries. Source: Data from Finland (a) are from Tuomilehto et al. 1999 [44] for 1965–1979, Harjutsalo et al. 2013 [45] for 1980–2006, and (b) from Parviainen et al. 2020 [31] for 2003–2018. Swedish data are from Hussen et al. 2013 [46], Norwegian data are from Joner and Søvik 1989 [47] and Skrivarhaug et al. 2014 [48]. Data for Western Australia are from Haynes et al. 2018 [49], Algerian data from Niar et al. 2015 [50], Polish data from Chobot et al. 2017 [51], Mexican data from Wacher et al. 2019 [52], and Japanese data for 1973–2001 from Kawasaki et al. 2006 [53] and for 2005–2012 from Onda et al. 2017 [54].

reaching almost 60 per 100 000 per year in 2006. After a peak in 2006, the incidence among children in Finland seems to have plateaued [45] and decreased [31] (Figure 4.3). In Sweden, data from the Swedish Childhood Diabetes Register suggested a possible plateau in incidence in 2006 [62], but other register data showed a continued increase up to 2009 [46]. Furthermore, Germany [63], Israel [64], the USA [65], Yorkshire, UK [66], and Shanghai, China [67] are examples of countries or areas with a continuing rise in incidence up to recent years.

In Western Australia (Figure 4.3) there was an increasing incidence from 1985 to around 2000–2002 when the incidence plateaued until 2016 [49]. Nationwide data showed a declining incidence between 2002 and 2017 [61]. Superimposed on these trends in Australia, there has been a cyclical pattern with approximately 3–5-year cycles [49, 61].

Cyclical patterns have been observed elsewhere, but there does not seem to be a general pattern [7]. In Norway, there was a plateau in the type 1 diabetes incidence from 2004 to 2012 [48], but the incidence rose up to 2013 and the overall pattern is consistent with a long-term increase [7]. When stratified by sex and age groups, the year-to-year variation in most studies becomes large and trends should be interpreted with caution. From the observed long-term trends (Figure 4.3), reliable predictions of incidence more than a few years into the future are difficult.

Variation in incidence within countries including by ethnicity

In several countries, marked within-country variations in the incidence of type 1 diabetes have been reported, even in relatively homogeneous populations. There is also marked ethnic variation, generally in line with the differences in countries or regions already discussed, and some geographical differences may be in part due to differences in the distribution of ethnic groups. Potential methodological problems should be considered when making inferences based on epidemiological studies of different ethnic groups and immigrants. These include differential ascertainment and definition of ethnic group, underestimation of the base population in some ethnic groups, genetic admixture, and possible heterogeneity in clinical presentation [68, 69]. Among childhood-onset cases, however, it seems that the large majority, even in Japan [53], have classic autoimmune type 1 diabetes.

Historically, the incidence of type 1 diabetes has been higher in populations of European origin, particularly those living in Europe, than among populations of non-European origin [68, 70]. The incidence rates of type 1 diabetes in most South American studies with standardized registries seem to be much lower than among Latino people in the USA and lower than the incidence rate of Spaniards living in Spain [68]. Data from the USA show clear ethnic differences in incidence and time trends for type 1 diabetes among youths during 2002–2015 (Figure 4.4). The highest incidence was among white youths (25–27 per 100 000 per year), while Black and Hispanic youths had similar rates, around 15–17 per 100 000 per year by 2010, and among Black youths the rate increased more sharply to nearly 20 per 100 000 in 2015 [38]. Asian Pacific Islanders and American Indian youths had a much lower incidence at ~5–10 per 100 000 per year. Other studies have indicated that the differences in incidence among ethnic groups in the USA are less dramatic, at least for some groups in some regions [6, 70]. Many ethnic groups in the USA have considerable admixture with people from European ancestry that may dilute potential differences between ethnic groups.

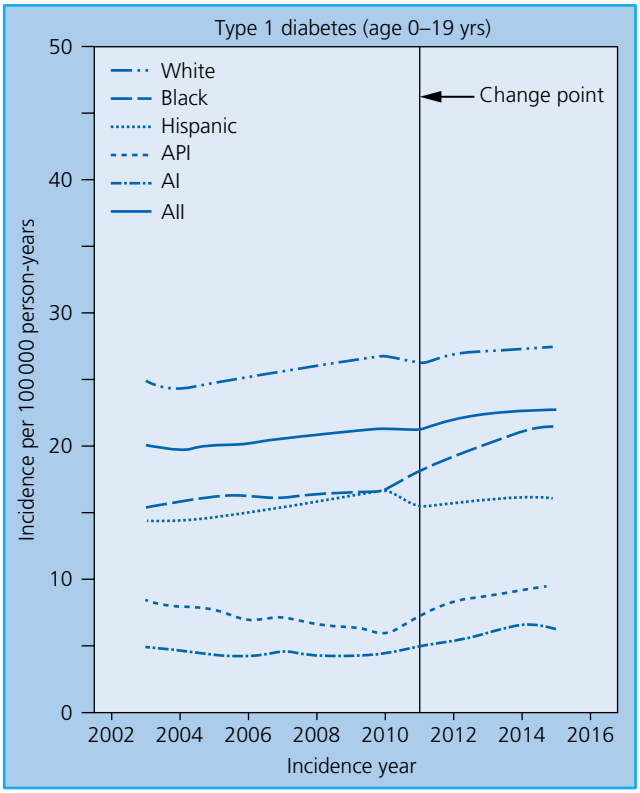

Figure 4.4 Time trends in incidence of type 1 diabetes by ethnicity in youth aged 0–19 years in the USA. Source: Reproduced from Divers et al. 2020 [38]. Data are from the SEARCH study – in geographically defined populations in Colorado, Ohio, South Carolina, Washington, and Kaiser Permanente Southern California health plan enrollees. API denotes Asian and Pacific Islanders; AI denotes American Indians.

Up to 1.5-fold differences in incidence have been described among regions within Finland, Sweden, and Norway [71–73]. In Italy during 1990–2003, the incidence rate among children varied from approximately 40 per 100 000 per year on the island of Sardinia, to 11–19 per 100 000 per year in regions of northern (mainland) Italy, and 8–12 per 100 000 per year in the central-southern part of mainland Italy [74]. Sardinia's population history is different to that of the rest of Italy. Children born in families who moved to mainland Italy from Sardinia kept their high type 1 diabetes incidence [75]. In New Zealand, the 1.5-fold higher incidence among children in the South Island compared with that in the North Island was largely explained by the 4.5 times higher incidence among children of European origin compared to that among Māoris, whose proportion is higher in the North Island [76]. In China, there was a 12-fold geographical variation (0.13–1.61 per 100 000), generally with higher incidence in the north and the east. In addition, there was a sixfold difference between the Mongol (1.82 per 100 000) and Zhuang (0.32 per 100 000 per year) ethnic groups [77]. In the nationally representative 10% sample of the Chinese population studied during 2010–2013, there was a 3.6-fold variation in incidence among 13 large regions, ranging from 3.6 in Harbin to 1.19 in Shanghai [10].

Considering immigrants as a single group, the time trends in incidence differed significantly from ethnic Swedes from the late 1980s onwards [46]. In Israel, there was a parallel increase over time, but consistently lower incidence in childhood-onset type 1 diabetes among non-Jews (mainly Palestinians) than among Jews

during 1997–2010 [64]. There also seemed to be a systematically lower incidence among South Asian than among non-South Asian children in Yorkshire [66]. The incidence of type 1 diabetes among children of immigrant parents in Germany, Sweden, and mainland Italy correlates with the incidence in the country or region of origin of their parents, whether the incidence in the country of origin was higher or lower [75, 78, 79]. The incidence among immigrants from Pakistan to the UK (or their children), however, was similar to that among the native Britons [80, 81], despite the very much lower incidence recorded in Karachi, Pakistan [6].

In summary, although there are clear ethnic differences in the incidence of type 1 diabetes and strong evidence for a role of genetic factors, some of the studies mentioned also suggest a possible role for yet unidentified environmental factors.

Seasonal variation in diagnosis of type 1 diabetes

Several studies have reported a peak in the number of cases diagnosed in the autumn and winter, and a smaller proportion of cases diagnosed in the spring or summer, consistent in both the northern and southern hemispheres [13, 32]. Although reasonably consistent, there is some variation in exact peak and nadir between countries, age groups, sexes, and periods. Generally, the degree of seasonal variation is stronger among those diagnosed at age 10–14 years than in younger children (Figure 4.5) [32]. Different methods have been used in the analysis of seasonal variations, and often with data covering relatively short periods of time and a limited number of cases; the results are therefore not necessarily comparable. Interpretation of seasonal variation must be carried out in light of the long and variable pre-clinical period in type 1 diabetes, and it is speculated that viral or other periodic factors have a role in the timing of the precipitation or onset of the disease in susceptible individuals who would develop it sooner or later.

Familial clustering and twin studies

Besides providing clues regarding the relative importance of genetic and non-genetic factors in the aetiology of disease, data on risk of type 1 diabetes among people with affected relatives may also aid the clinician in counselling family members of newly diagnosed individuals. Around 80–90% of persons with newly diagnosed type 1 diabetes do not have any affected siblings or parents, but first-degree relatives of a person with type 1 diabetes are at increased risk. By the age of 20 years, approximately 4–6% of siblings of type 1 diabetes probands develop type 1 diabetes in European-origin populations [82–84], compared with around 0.2–1.0% in the corresponding background populations. The offspring of affected fathers have a 1.5–3 times increased risk of type 1 diabetes compared with the offspring of affected mothers [85, 86]. By 20 years of age, 5–8% of the offspring of men with type 1 diabetes, but only 2–5% of the offspring of women with type 1 diabetes, are affected. There is currently no accepted explanation for this phenomenon.

Given the well-established effect of genetic factors, it is no surprise that the concordance rate for type 1 diabetes in monozygotic twins is much higher than that in dizygotic twins [87, 88]. In one study from North America, the cumulative risk 10 years after onset in the proband (diagnosed before age 40 years) was ~25% in monozygotic twins and ~11% in dizygotic twins [89]. Corresponding 10-year cumulative risks from Finland were estimated as 32% for

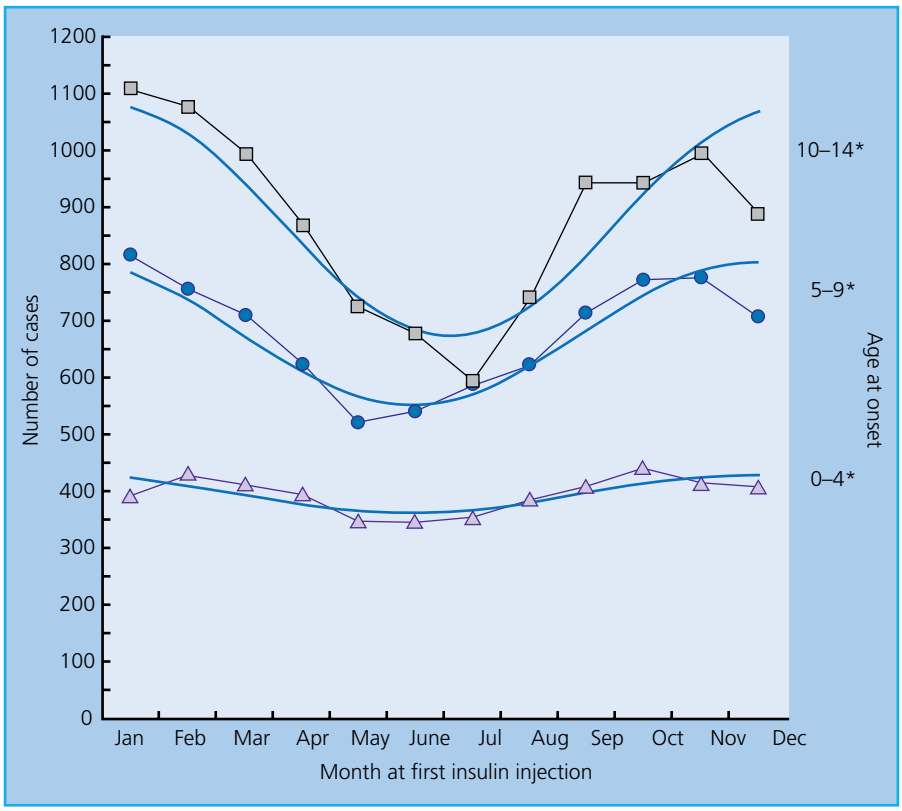

Figure 4.5 Seasonal variation in diagnosis of type 1 diabetes among >22 000 children diagnosed 1989–1998 in European centres, by age at onset. *Age (years) at first insulin injection. Source: Reproduced from Green and Patterson 2001 [32], with permission from Springer-Verlag.

monozygotic twins and 3.2% for dizygotic twins [88]; comparable estimates were also found in the Danish twin registry, although the exact age at onset was unknown [87]. In general, the risk for the co-twins was higher and the discordance time shorter the earlier the type 1 diabetes diagnosis in the proband [88–90]. In a long-term follow-up of discordant monozygotic twins from the USA and the UK, more than 50% of monozygotic pairs remained discordant for type 1 diabetes (Figure 4.6) [90]. Because monozygotic twins share 100% of their genomic DNA, this suggests that genetic susceptibility alone is in most cases insufficient for the development of disease.

Despite the relatively high proportion of monozygotic twins being discordant for clinical type 1 diabetes, many of the co-twins without diabetes of individuals with type 1 diabetes develop islet autoimmunity [91]. Together with the limited variation in prevalence of positivity for islet autoantibodies between countries [60] and animal studies suggesting a two-stage disease process [92], this supports the idea that environmental factors may have an important role in the progression from islet autoimmunity to overt disease.

Environmental risk factors for type 1 diabetes: clues from epidemiological studies

The time trends described earlier must be ascribed to changes in the environment, even in the event that the increase is brought about by a change in the age distribution. Some of the variation in incidence rates between European countries can be explained by differences in the frequency of HLA susceptibility genotypes [93], but not all [94]. The proportion of people with newly diagnosed type 1 diabetes who carry the highest-risk genotype (DR3-DQ2 per DR4-DQ8) has decreased over three to four decades, while moderate-risk and low-risk genotypes have become more common among those with type 1 diabetes [95]. It may be speculated that increased exposure to some risk factor or decreased exposure to some protective factor has caused more individuals with moderate-risk (*permissive*) genotypes (e.g. either DR3-DQ2 or DR4-DQ8, but not both) to develop type 1 diabetes in recent years. Although there is overwhelming evidence for an essential role of genetic factors in the aetiology of type 1 diabetes, available evidence strongly suggests that some yet unknown non-genetic factors are also involved.

In general, environmental factors may be envisioned to have a role in:

- Initiating the autoimmune disease process;
- Modulating the progression from islet autoimmunity to clinical type 1 diabetes; or
- *Precipitating* disease in individuals with advanced pre-clinical disease.

Little is known about the initiation of autoimmunity in humans, but breakdown of immunological self-tolerance is thought to be involved. An incidence peak in islet autoimmunity in the second year of life and early seroconversion for islet autoantibodies among children who develop type 1 diabetes suggest that potential environmental factors can operate very early in life [96]. Limited geographical variation in the prevalence of islet autoimmunity despite the large differences in incidence of type 1 diabetes between countries suggests that environmental factors may influence the progression from islet autoimmunity to type 1 diabetes [60]. However, this is difficult to reconcile with the observation that in the long run, most children with multiple autoantibodies go on to develop type 1 diabetes [2]. Geographical differences in the prevalence of advanced islet autoimmunity can be confounded by the fact that prevalence is influenced by both incidence of islet autoimmunity and rate of progression to type 1 diabetes. The multinational TEDDY study investigated both. With standardized recruitment of children with increased genetic risk, there were modest differences in both incidence of islet autoimmunity and progression from autoimmunity to type 1 diabetes between Finland,

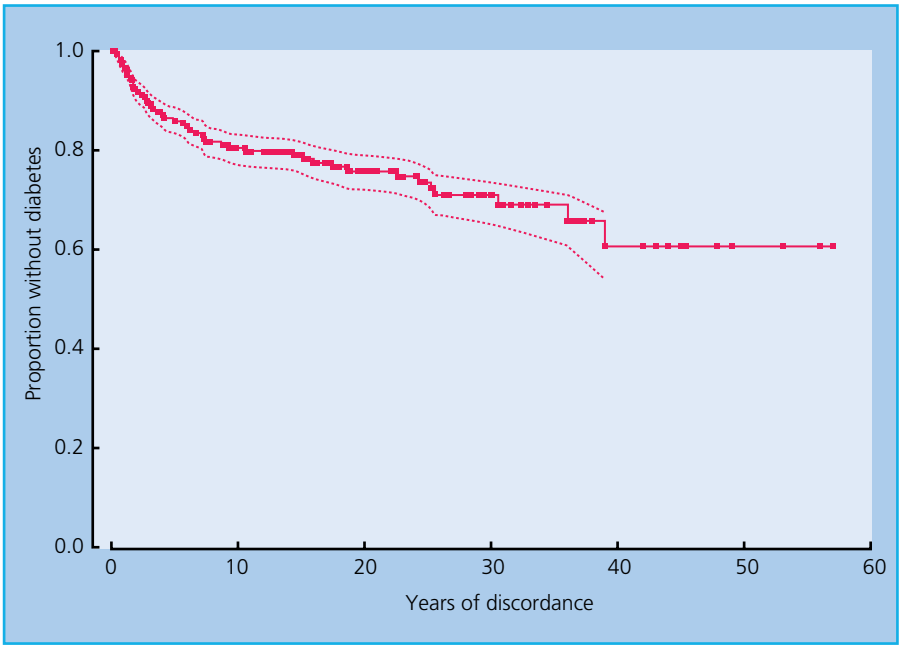

Figure 4.6 Diabetes-free survival in monozygotic twins without diabetes whose co-twin had type 1 diabetes, after several years of follow-up. Dotted lines represent 95% confidence intervals. Source: Reproduced from Redondo et al. 2001 [90], with permission from Springer-Verlag.

Germany, Sweden, and the USA [3, 97]. *In vitro* experiments have suggested that active insulin-secreting β cells hyperexpress islet autoantigens such as GAD and are more susceptible to toxic effects of the cytokine interleukin-1 β [98]. It may be speculated that factors that increase the stress on β cells may non-specifically contribute to the precipitation of clinical disease [98]. This includes insulin resistance or other mechanisms implied in infections, puberty, and growth spurts. Insulin resistance is difficult to measure reliably in children, but measures of insulin resistance relative to first-phase insulin response during an intravenous glucose tolerance test are predictive of progression to type 1 diabetes [99]. A 2020 review found that among the potential aetiological factors studied so far, no single factor has been convincingly associated with risk of type 1 diabetes with a magnitude of association and changing exposure pattern over time compatible with explaining the changing epidemiology of type 1 diabetes over the past decades [100]. More likely, several factors combine to explain the changing incidence, or yet unknown factors are responsible. Methodological problems such as measurement errors, confounding, and selection bias should also be kept in mind when reviewing aetiological studies.

Specific putative environmental factors

Microbes

There is a large body of literature linking infections and type 1 diabetes, including plausible mechanisms involved, but the link has not been unequivocally established as causal in humans [101–103]. Studies vary in design, from *in vitro* studies [104], experiments with various animal models [105], studies of individuals with disease including of pancreatic tissue [104, 106–109], and epidemiological case–control and cohort studies [13, 110–112]. Congenital rubella syndrome has been associated with a several-fold increase in the incidence of type 1 diabetes [113]. Although not contributing to the incidence of type 1 diabetes in most countries today because of vaccination, this observation has been cited as a proof of principle that intrauterine factors and viral infections in general can influence the risk of type 1 diabetes in humans. However, the consistency of the available evidence and the absolute risk of type 1 diabetes associated with congenital rubella may have been overstated [114, 115].

Several early studies based on assays for antibodies to enteroviruses in cases with type 1 diabetes and controls initially seemed promising, but systematic review of the data showed too much heterogeneity in methodology and results to draw any firm conclusion [110]. Prospective study design and detection of enterovirus RNA represent important contributions to the methodology of such studies in recent years, but a careful review of available data shows that they are not consistent across studies [112].

Increased risk of childhood-onset type 1 diabetes has been associated with evidence of maternal enterovirus infections during pregnancy in some studies, but not in all [112, 116]. Using both serum enterovirus antibodies and RNA as indications of postnatal infection, prospective studies did not find consistent associations between enterovirus and islet autoimmunity [112]. Earlier studies suggested that the presence of virus particles in the blood was more strongly correlated to type 1 diabetes than their presence in the stool [111, 112, 117]. A recent analysis of the DIPP study from Finland reported an association between faecal enterovirus shedding and the later risk of islet autoimmunity [118]. The multinational TEDDY study found that long duration of faecal shedding of enterovirus B was associated with a higher risk of islet autoimmunity, but not with type 1 diabetes [119]. Recently, metagenomics approaches with next-generation sequencing of the virome have been used in epidemiological studies of islet autoimmunity or type 1 diabetes, but they have been small, methods have varied, and they have suggested at best only weak associations, mostly with enteroviruses [120].

An immunohistochemical study of stored sections of pancreatic biopsies obtained post mortem in young individuals with recent-onset type 1 diabetes found that the β cells of multiple islets stained positive for enterovirus capsid protein VP1 in 44 of 72 cases, while few controls stained positive [108]. This study substantiated previous evidence based on a few individuals [106, 107] and indicated problems with the methods used in a previous study where no such evidence was found [121]. Based on early data [106], the coxsackie B4 serotype of human enterovirus has been suspected to be particularly diabetogenic. Technical difficulties in the detection and interpretation of low quantities of virus particles remain, but a recent study found signs of enterovirus by multiple techniques and in different labs, in fresh pancreatic tissue obtained from six young adults with newly diagnosed type 1 diabetes [109]. Recently, application of serotype-specific neutralizing antibody tests to the prospective DIPP study suggested a novel association between the coxsackie B1 serotype and risk of islet immunity [122]. In this study, there tended to be an inverse association between coxsackie B4 and risk of islet immunity [122], an association in the opposite direction to what has been suggested in other studies.

The so-called *hygiene hypothesis* comes in different versions, but essentially proposes that reduced microbial exposure in many populations over the past few decades has caused a concomitant increase in incidence of immune-mediated diseases, including type 1 diabetes [123]. Some infections and microbial agents reduce the incidence of autoimmune diabetes in experimental animals [124]. Epidemiological studies have investigated non-specific infections and infectious symptoms, but the results have been inconsistent. Daycare attendance is usually associated with increased exposure to microbial agents, and a recent meta-analysis concluded that there is some evidence for a lower risk of type 1 diabetes among children who attended daycare centres early in life, although the results were not sufficiently homogenous to allow a strong conclusion [125]. Enterovirus infections are common and the frequency of infection has decreased with improved hygiene in recent decades, opposite to the trend seen for type 1 diabetes. It has been postulated that the increasing incidence of type 1 diabetes in children may in part be explained by decreased protection from maternal enterovirus antibodies [126]. A direct test of this hypothesis is still lacking. Antibiotics modify the gut microbiota at least temporarily. However, use of antibiotics is also a proxy for infections, and infections themselves may influence immunity and the composition of the microbiota. Most large studies have not found any consistent association between use of antibiotics in childhood or by pregnant women and subsequent risk of islet autoimmunity or type 1 diabetes [127–134]. However, a weak but significant positive association was found in a study from Sweden [135], and for broad-spectrum antibiotics in a Danish study [129], with relative risks of around 1.1–1.2, but stronger in children born by caesarean section. The gut microbiota is excessively complex and has been hypothesized to influence type 1 diabetes based on relatively small studies [136]. The largest prospective study in the field found few or no significant

differences between cases of islet autoimmunity or type 1 diabetes and controls [137, 138].

Regular childhood vaccinations are not associated with risk of type 1 diabetes, although this is a challenging research question in case–control or cohort studies in populations where the large majority of infants are vaccinated [139]. While rotavirus is a common cause of early childhood gastroenteritis, vaccinations against this pathogen were introduced in many countries in the 2000s. Comparing birth cohorts before and after the introduction, an association with type 1 diabetes was not seen in Finland [140], but a suggestive inverse tendency was reported from Australia [141] and the USA [142]. A randomized trial of rotavirus vaccination in Finland with later follow-up for type 1 diabetes in a subset of participants did not find any significant difference in the incidence of type 1 diabetes [143].

To summarize, there are many promising observations on microbes. However, the current evidence that infections have an important and causal role in human type 1 diabetes is inconclusive. Designing a vaccine that covers the relevant type or types is challenging, but work on an enterovirus vaccine is in progress [144]. Others have suggested it may be possible to develop a vaccine that can reproduce the potential beneficial effects of virus infections (cf. the hygiene hypothesis) regardless of the existence or identification of one or a few diabetogenic viral serotypes [124]. It has been hypothesized that Covid-19 may increase the risk of type 1 diabetes. The future will bring more data on the topic, but at least some countries experienced a higher incidence of type 1 diabetes during the Covid-19 pandemic than in earlier years [145]. Three nationwide studies based on complete population register linkages, each with over one million children and adolescents, have investigated the potential association between a positive SARS-CoV-2 polymerase chain reaction (PCR) test and risk of type 1 diabetes 30 or more days later in the period 2020 to early 2022. No significant association was reported in Scotland (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.62 to 1.21 for 0–34-year-olds and consistent results in those <16 years old [146]) and in Denmark (HR 0.85, 95% CI 0.70 to 1.04 [147]). In Norway, there was a significantly increased risk (HR 1.63, 95% CI 1.08 to 2.47 in <18-year-olds [148]). The reasons for the discrepant results are unclear, but it is important to note that the absolute risk of type 1 diabetes after SARS-CoV-2 infection was low (0.13% in the infected vs 0.08% in those with no registered infection). Future studies and longer follow-up will likely provide more answers.

Toxins and environmental chemicals

Several environmental chemicals may influence the immune system and potentially the risk of type 1 diabetes [149]. The rodenticide Vacor has been associated with type 1 diabetes in humans after ingestion of large doses [150]. There are structural and mechanistic similarities between Vacor and streptozotocin and alloxan [150]. Some epidemiological studies have assessed intake of nitrates and nitrites, which may be converted to N-nitroso-compounds, but most studies have used ecological study designs and assessed levels in community drinking water, which is probably a poor indicator of total exposure. In a case–control study nested within a cohort of pregnant women, persistent organochlorine pollutants in stored sera were not associated with later risk of type 1 diabetes in the offspring [151]. If anything, there was a tendency towards an inverse association. More recent studies have also attempted to link air pollution and various environmental chemicals to risk of type 1 diabetes, although the evidence remains inconclusive [152]. In conclusion, few high-quality studies are available on the potential influence of environmental chemicals on type 1 diabetes incidence in the population, and there is currently little direct evidence for an important involvement of such factors in human type 1 diabetes.

Nutritional factors

Several possible plausible mechanisms have been proposed to link dietary factors to type 1 diabetes, including *molecular mimicry* and a detrimental effect of bovine insulin in cow's milk [153].

Infant feeding

A reduced risk conferred by prolonged breastfeeding or delayed introduction of cow's milk has been suggested in many case–control studies, but most of these studies were susceptible to recall bias and the issue is controversial [154]. Large prospective studies have found no clear association between the duration of exclusive or total breastfeeding and risk of islet autoimmunity or type 1 diabetes [155–157]. It is difficult to differentiate the role of the duration of breastfeeding versus the time of introduction of weaning foods in observational studies. However, the TRIGR trial tested the hypothesis that delaying the introduction of intact cow's milk proteins (regardless of breastfeeding duration) prevented type 1 diabetes, although it did not show any efficacy [158].

Vitamin D

The immunomodulatory effects of vitamin D and preventive effect of high doses of vitamin D on diabetes development in experimental animals have been documented with early intervention [159]. The consensus among large-scale human studies linking maternal or newborn vitamin D status (circulating 25-hydroxyvitamin D) to the risk of type 1 diabetes in the offspring is now that there is no association [160–162]. For vitamin D status in early life, despite mixed results from previous smaller studies, recent longitudinal studies in high-risk cohorts have linked higher levels with a slightly lower risk of islet autoimmunity or type 1 diabetes [163, 164]. However, a large Mendelian randomization study did not find any significant association between vitamin D status and type 1 diabetes, providing some evidence against a causal relation between the two [165].

In summary, the causal role of nutritional factors in the aetiology of type 1 diabetes remains uncertain.

Perinatal factors and postnatal growth

Offspring of mothers without diabetes aged 35 years or more when giving birth have an approximately 20–30% increased risk compared with offspring of mothers who are 25 years or less [166, 167]. Results for birth order and for paternal age have not been consistent [166, 168, 169]. Birth by caesarean section was recently associated with an approximately 20% increased risk of type 1 diabetes in children according to a meta-analysis of 20 published studies [170]. Although there is some potential for selection bias in the case–control studies, and the mechanism is unknown, it was speculated that delayed colonization of the infant's intestine associated with caesarean section may be involved. On the other hand, a recent study of discordant sibships did not find any association between caesarean section and type 1 diabetes [171].

Increased birth weight has been associated with a relatively weak but significant increase in risk of childhood-onset type 1 diabetes in

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large-cohort studies based on linkage of population registries, independent of maternal diabetes and other potential confounders [172]. There are also studies reporting no significant association, but these were generally smaller case–control studies. Birth weight is certainly only a marker of some other phenomenon and the mechanisms involved remain to be defined.

Associated factors such as postnatal growth or excess body weight might be of relevance. Studies have indicated that children developing type 1 diabetes are taller, heavier, or gain more weight or height prior to diagnosis compared to their peers [173]. However, there was substantial heterogeneity between studies in methodology and results, such as age at measurement of body size, which body size or growth measurement was associated with type 1 diabetes, and how data were analysed statistically. Many of the published studies were case–control studies, which are prone to selection bias, although a large Mendelian randomization study found evidence for a causal effect of childhood body mass index on risk of type 1 diabetes [174]. Also, two recent large-scale cohort studies found that for each standard deviation (approximately 1 kg) increase in weight or weight gain up to age 12 months, the risk of type 1 diabetes [175] or multiple islet autoantibodies [176] increased by approximately 20%.

In summary, environmental factors may influence individuals differently, depending on the genetic background, although direct evidence for specific gene–environment interactions from humans is scarce. No specific environmental factor has been identified thus far. Taking into account the multifactorial nature of type 1 diabetes, specific environmental risk factors with sufficiently large impact to be of clinical importance and detectable in epidemiological studies may not exist. However, identification of potential environmental risk factors and their role in the disease process is important in the potential prevention of type 1 diabetes in the future, and the lack of consistent findings may reflect a lack of properly conducted prospective studies.

Mortality

Before the discovery of insulin in 1922, type 1 diabetes led to almost certain death soon after its onset. After the initiation of insulin replacement therapy, a dramatic improvement in survival occurred. Another major improvement in survival occurred in people diagnosed with diabetes in the 1950s [177]; however, even today type 1 diabetes is associated with an approximately two- to eightfold higher mortality rate than that in the background population [178–180] (Figure 4.7). Relative mortality varies between countries and periods. Also shown in Figure 4.7 are the absolute mortality rates, which tend to correlate with the standardized mortality ratio (SMR). For instance, the SMR for individuals with type 1 diabetes in Finland was lower than in Lithuania, Estonia, and Japan [181, 182]. A higher mortality has been reported in African American compared to white individuals with type 1 diabetes in the USA, and this difference seems to be attributable to acute complications [183].

In Europe, short-term mortality was two times higher in individuals followed from diagnosis of type 1 diabetes in childhood than in the respective general populations, with variation in the SMR from about 1.1 to 4.7 in different countries [184]. In a nationwide cohort of people with type 1 diabetes in Norway followed from onset before 15 years of age and up to 40 years' duration (mean 17 years), the SMR was 3.6 [179]. In a UK cohort of more than 7000 prevalent cases of type 1 diabetes with a mean age of 33 years at baseline, the SMR after up to 7 years of follow-up (mean 4.5 years) was 3.7 [185]. Many studies have reported that the SMR varies with age and with diabetes duration, or both, but results are not consistent among studies.

Ascertainment of cause of death in young people with type 1 diabetes is difficult, but around one-third of the early deaths in the recent European multicentre study were attributable to diabetic ketoacidosis, while about half of the deaths seemed unrelated to

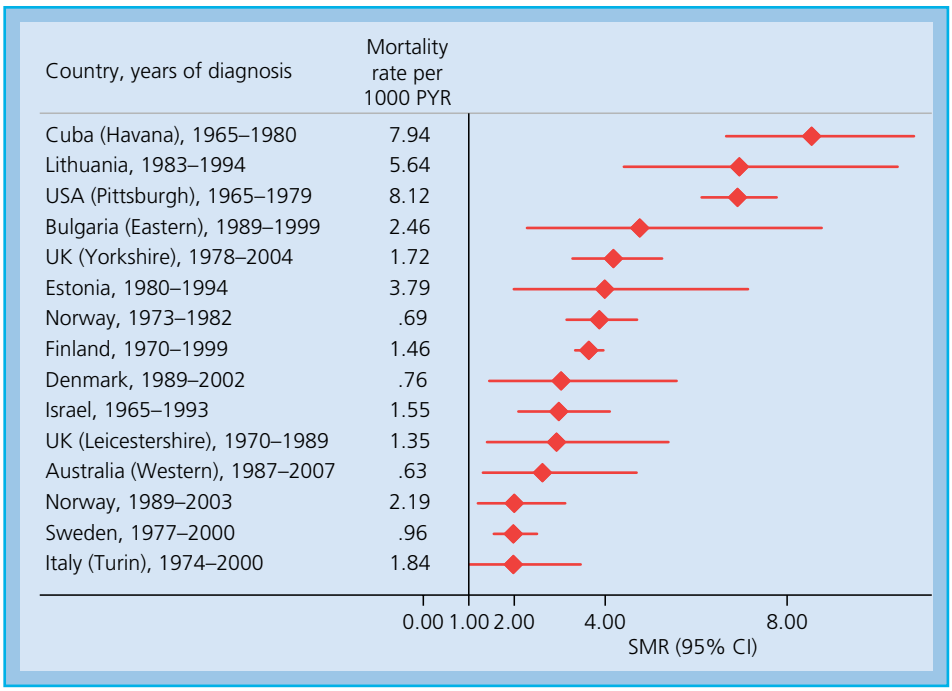

Figure 4.7 Standardized mortality ratios (SMRs) for individuals followed from diagnosis of childhood-onset type 1 diabetes. Source: Data are from different studies, summarized by Morgan et al. 2015 [178]. Only studies with at least 10 observed deaths are shown here. An SMR of 1.0 means a mortality rate among persons with type 1 diabetes that is equal to that in the background population for the same age, sex, and calendar period. Studies were sorted by the earliest year of diagnosis of type 1 diabetes, and secondarily by SMR. There were differences in duration of follow-up and other minor methodological differences between studies. CI, confidence interval; PYR, person-years at risk.

diabetes [184, 186, 187]. After about 10–15 years of diabetes duration, microvascular and macrovascular chronic diabetes complications start to make an impact, and after about 30 years of age cardiovascular causes become increasingly important [188]. Relative mortality from cardiovascular causes is in most populations higher in women than in men [189]. SMRs of 8–40 have been reported for cardiovascular causes of death in individuals with type 1 diabetes, and depend strongly on the presence of nephropathy [180, 188, 190–192].

A few recent data are available on mortality due to Covid-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). In a study of 264 000 individuals with type 1 diabetes in the UK, the risk of in-hospital mortality with Covid-19 in early 2020 was threefold higher than among people without diabetes [193]. Only 6 of 464 observed deaths occurred in individuals aged below 40 years. However, while the absolute risk of death increased with age, the relative risk of death in persons with type 1 diabetes tended to be higher in the younger age groups. Mortality was around sixfold higher in 50–59-year-olds compared with people of the same age without diabetes. Higher glycated haemoglobin (HbA_{1c}) was associated with significantly higher Covid-19–related mortality in individuals with type 1 diabetes, after adjusting for other risk factors [194].

Better glycaemic levels and improved risk factor management, such as lowering of blood pressure and lipids, are associated with reduced risks of late complications and improved survival [195]. Long-term follow-up in the DCCT and EDIC studies showed that multiple daily insulin injections (today's standard mode of treatment) compared to less intensive insulin treatment for 1–15 years resulted in a significant reduction in total mortality [196]. Nevertheless, a large proportion of individuals with type 1 diabetes have suboptimal HbA_{1c} levels. Despite the relationship between higher HbA_{1c} and increased mortality, a Swedish study found that even those with low HbA_{1c} seem to have a significantly higher mortality than people without diabetes [180]. In line with the impression that treatment is gradually improving, people diagnosed with type 1 diabetes in more recent years seem to have lower short-term mortality compared with individuals diagnosed in earlier time periods [197–199]. Many authors have estimated the loss in life expectancy due to type 1 diabetes at around 8–18 years, depending on time period, sex, and age at onset [189, 200, 201].

Because individuals with type 1 diabetes have higher mortality than the background population at all ages, and life expectancy is a summary measure of mortality in a current period across all age groups, it is perhaps unsurprising that the estimated reduction in life expectancy is greater for those with young age at onset [189, 202]. Despite the apparent ease of interpretation of loss in life expectancy, this estimate is a complex summary applicable only to hypothetical individuals who probably do not exist [202]. Nevertheless, despite continuing improvement in care, a major gap in mortality compared to the general population remains in recent large-scale studies from high-income populations. In many low- and middle-income countries, mortality in people with type 1 diabetes is very high [203]. A continuing challenge is also deaths among those with undiagnosed type 1 diabetes and individuals without access to insulin and health care in low- and middle-income countries.

Conclusion

Type 1 diabetes is one of the most common chronic diseases diagnosed in childhood, but the condition can occur at any age. Its incidence varies drastically between populations and even within populations. Type 1 diabetes has a strong genetic component and familial clustering, but the majority of cases have no affected siblings or parents. Only a minority of carriers of the susceptibility genes develop type 1 diabetes. The incidence of type 1 diabetes is increasing in most studied populations at an average rate of approximately 3–4% per year, but has plateaued or even decreased in some countries recently. Some environmental factors may contribute to the development of diabetes, but no definite causal environmental factor for type 1 diabetes has yet been identified.

Type 1 diabetes was a fatal disease before the insulin era. Although mortality in individuals with diabetes has drastically decreased, both acute and late complications lead to increased morbidity and premature mortality in type 1 diabetes. Primary prevention of type 1 diabetes would be the only solution to these problems, but unfortunately no practical preventive measures are currently available.

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5 Epidemiology of Type 2 Diabetes

Ronald C.W. Ma[1,2,3] and Peter C.Y. Tong[4]

[1] Division of Endocrinology and Diabetes, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, SAR, China

[2] Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong, SAR, China

[3] Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong, Hong Kong, SAR, China

[4] The Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong, SAR, China

Key points

- The prevalence of type 2 diabetes continues to increase worldwide.
- Approximately 537 million people worldwide were living with diabetes in 2021, making it one of the commonest non-communicable diseases globally.
- The largest increase is observed in regions with rapidly developing economies and urbanization.
- The ageing population, with an increase in the proportion of people aged >65 years in most countries, has contributed significantly to this increase in prevalence.
- The age of onset of diabetes is decreasing in many countries, giving rise to an increasing proportion of young people of working age being affected by the disease.
- Several risk factors are known to be associated with an increased risk of type 2 diabetes. Many of these risk factors are associated with a Westernized lifestyle and increase with urbanization, although novel environmental risk factors have emerged.
- Areas with a high ratio of impaired glucose tolerance to diabetes are at an earlier stage of the diabetes epidemic, and thus may be a particular target for preventive strategies.
- The Pacific Islands and Middle East are the regions with the highest diabetes prevalence rates.
- The largest increase in diabetes prevalence is predicted to occur in Africa.
- Diabetes is associated with approximately twofold increased mortality in most populations, with the excess risk decreasing with increasing age.
- The increase in diabetes prevalence, particularly among young adults, along with the increased morbidity and mortality associated with microvascular and macrovascular complications, is likely to lead to an escalation of healthcare costs and loss of economic growth.
- Recent data suggest stable or declining diabetes incidence in some high- and middle-income countries where data are available.
- Prevention efforts require widespread public education and coordinated multisector efforts to encourage physical activity and a healthy diet.
- Maternal health and the intrauterine environment have also emerged as an important window of opportunity for prevention.
- Remission of type 2 diabetes is possible through intensive lifestyle modification or metabolic surgery, highlighting the benefits of weight loss. This may complicate epidemiological analyses on diabetes prevalence.

Type 2 diabetes is one of the commonest forms of chronic disease globally and few societies or ethnic groups are spared. It accounts for ~95% of cases of diabetes in most populations [1]. In 2021, the International Diabetes Federation (IDF) estimated that 536.6 million people worldwide had diabetes, of whom 75% live in low- and middle-income countries. Globally, among those aged 20–79 years, ~10.5% had diabetes, of whom an estimated 44.7% remain undiagnosed. The highest number of people with diabetes was in the Western Pacific region, with 205.6 million, and the region with the highest prevalence rate, at 16.2%, was the Middle East and North Africa [2]. These estimates are generally in line with estimates from other sources. For example, the NCD Risk Factor Collaboration has estimated from 751 population-based studies, including 4.4 million participants, that the number of adults in the world living with diabetes in 2014 was 422 million [3].

The number of people with diabetes is expected to reach 783.2 million by 2045, an increase of 46% [2]. The largest increases have been in countries with rapidly growing economies, such as India and China, and the largest increase over the next two decades is predicted to occur in Africa. With the increasing consumption of high-energy food, and increasing adoption of sedentary lifestyles and urbanization, growing numbers of individuals are developing type 2 diabetes, and the age at which individuals are diagnosed is decreasing. Individuals exposed to longer periods of hyperglycaemia will undoubtedly have greater risks of developing diabetes-related complications. The potential healthcare costs and burden of diabetes in these regions will have a significant impact on the economic growth of these regions, as discussed in Chapter 3.

The epidemiology and prevalence of diabetes are partly determined by the diagnostic criteria used to diagnose diabetes, and these have

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been modified on several occasions. The diagnostic criteria for diabetes and impaired glucose tolerance are based on epidemiological evidence relating microvascular complications to specific degrees of hyperglycaemia, and the fasting glucose cut-off has been modified as new data emerged. These changes have major implications for the interpretations of current and future epidemiological studies on diabetes. In 1999, the diagnostic threshold of fasting glucose was lowered from 7.8 mmol/l (140 mg/dl) to 7.0 mmol/l (126 mg/dl). A fasting glucose level between 6.1 and 6.9 mmol/l (111–125 mg/dl) was considered to be *pre-diabetic* and the term *impaired fasting glucose* was used. Subsequent lowering of the *normal fasting glucose* level to 5.6 mmol/l (100 mg/dl) further increases the number of people with pre-diabetes. Impaired glucose tolerance, on the other hand, is another pre-diabetes state, which is only identified by oral glucose tolerance testing, with a post-load glucose level of 7.8–11.0 mmol/l (140–199 mg/dl). It is estimated that ~541 million people or 10.6% 20–79 years old have impaired glucose tolerance [2].

Risk factors for type 2 diabetes

Several risk factors are known to be associated with increased risk of type 2 diabetes, including increasing age, obesity (especially central obesity), dietary excess, dietary factors such as increased intake of animal fats and sugar-sweetened beverages, sedentary lifestyle, positive family history, history of gestational diabetes, polycystic ovary syndrome, presence of hypertension, hyperlipidaemia, or other cardiometabolic risk factors (Figure 5.1). Many of these risk factors are associated with a Westernized lifestyle and increase with increasing urbanization and mechanization. The recognition of the role of these factors in the pathogenesis of type 2 diabetes has led to recommendations for selective screening for type 2 diabetes in people with these risk factors [1, 2, 4].

Several large studies, including the Nurses' Health Study in the USA and the InterAct Study in Europe, have contributed to improved understanding of the role of dietary factors and the risk of incident type 2 diabetes. Dietary factors that increase the risk for type 2 diabetes include the following [5, 6]:

- Increased fat intake.
- Increased intake of red and processed meat.
- Consumption of fried food.
- Increased intake of white rice.
- Consumption of sugar-sweetened beverages.

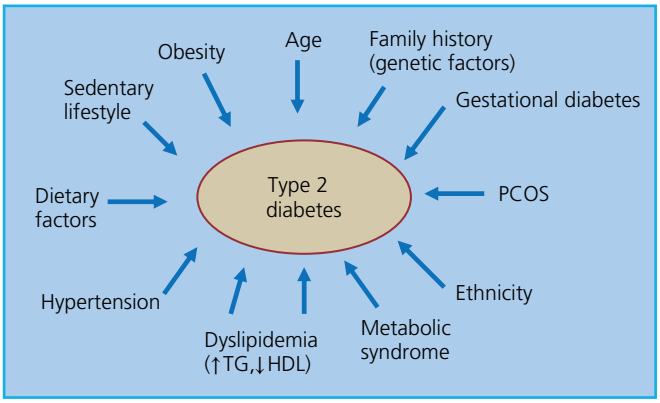

Figure 5.1 Risk factors in the development of type 2 diabetes. HDL, high-density lipoprotein cholesterol; PCOS, polycystic ovarian syndrome; TG, triglycerides.

Dietary factors that decrease the risk for type 2 diabetes include the following [5, 6]:

- Increased fruit and vegetable intake.
- A Mediterranean diet pattern.
- Consumption of fermented dairy products.
- Intake of oily fish.
- Drinking tea.

Obesity accounts for 80–85% of the overall risk of developing type 2 diabetes, and underlies the current global spread of the disease [7]. The risk of type 2 diabetes increases as the body mass index (BMI) increases above 24 kg/m^2, although the risk appears to be present with a lower BMI in Asians [8, 9]. Although central obesity is a particularly strong factor, it can impart further risk regardless of the overall level of general obesity. This obesity-related risk is more marked in certain ethnic populations such as Pima Indians, Black Africans, South Asians, Chinese, and other Asian populations [10–14], and may be related to increased visceral adiposity. Obesity, particularly central adiposity, is associated with insulin resistance and also β-cell dysfunction, partly through increased free fatty acids and lipotoxicity (Chapters 16–18). Obesity is also associated with other metabolic abnormalities such as dyslipidaemia and hypertension.

The clustering of some of the risk factors, namely hypertension, elevated blood glucose, elevated triglyceride, low high-density lipoprotein (HDL) cholesterol, and abdominal obesity, is termed the *metabolic syndrome*. Presence of the metabolic syndrome, according to the definition, is associated with a two- to fivefold increased risk of developing diabetes in most populations [15].

A positive family history is an important risk factor for type 2 diabetes. In the InterAct case–cohort study, a family history of type 2 diabetes was associated with a 2.7-fold risk of incident diabetes [16]. There have been advances in our understanding of the genetic basis of type 2 diabetes over the last few years, with more than 1000 genetic variants so far identified as being associated with type 2 diabetes (Chapter 12) [17]. Nevertheless, the identified genetic variants explain <10% of the heritability of type 2 diabetes. In the InterAct study, a genetic risk score composed of known genetic variants for type 2 diabetes explained only 2% of the family history–associated risk of the disease, suggesting that there are still unexplained factors that contribute to the association between family history and type 2 diabetes, including yet to be identified genetic factors, shared environment and behaviour, epigenetic factors, and possibly other factors [16]. Most of the known genetic variants for type 2 diabetes were identified in European populations. Although several type 2 diabetes–associated genetic variants have been identified in other populations, including East Asians and South Asians, our current knowledge of genetic variants associated with type 2 diabetes cannot explain the marked geographical and ethnic variations in diabetes prevalence [14, 18].

Traditional risk factors such as increasing age, adiposity, physical inactivity, dietary factors, positive family history, and presence of other cardiometabolic risk factors are well-recognized factors for diabetes and many are considered to be on the causal pathway. Current approaches to diabetes prevention are mostly focused on addressing these risk factors, in particular unhealthy diet and physical inactivity. In the prospective Whitehall II study, it was estimated that traditional modifiable risk factors such as health behaviour and obesity, when measured repeatedly over time, explain approximately half of the social inequalities in incidence of type 2 diabetes [19].

Emerging risk factors

Sugar-sweetened beverages

Consumption of sugar-sweetened beverages is now recognized as an important contributor to the recent rapid escalation in obesity and diabetes [20,21]. Sugar-sweetened beverages include carbonated soft drinks, fruit juices, iced tea, and energy and vitamin water beverages, and are similar in having high sugar content, low satiety, and low nutritional value. The intake of such beverages has increased markedly over recent decades, and consumption trends often mirror those of obesity and diabetes prevalence in different parts of the world [22]. Sugar-sweetened beverages contain added sugars in the form of fructose, chronic exposure to which can lead to hepatic steatosis, insulin resistance, central obesity, and metabolic abnormalities [23].

Decreased sleep

In addition to changes in diet and physical activity, it is increasingly recognized that there is a U-shaped relationship between sleep duration and diabetes risk, with short sleep duration, another facet of our modern lifestyle, being an important contributor to the increasing prevalence of type 2 diabetes. Early seminal work highlighted the detrimental effects of sleep deprivation on glucose tolerance and insulin sensitivity [24]. Subsequent cross-sectional studies have suggested an association between short sleep duration and diabetes [25] and obesity [26]. In a prospective study of >70 000 women in the Nurses' Health Study, short sleep duration was associated with a ~57% increase in diabetes risk over the 10-year study period [27]. Similar data were obtained from the First National Health and Nutrition Examination Survey (NHANES I), which noted that people with a sleep duration of ≤5 hours had a 47% increase in incident diabetes over a 10-year period [28]. The exact mechanism whereby sleep restriction increases diabetes risk is unclear, although it may be related to activation of the sympathetic nervous system, decrease in cerebral glucose utilization, changes in the hypothalamic–pituitary–adrenal axis, and other neuroendocrine dysregulation [28]. In addition to short duration, other sleep disturbances and altered circadian rhythm, for example during shift work, are associated with an increased risk of diabetes [29].

Depression and treatment of depression

There is a bidirectional relationship between depression and diabetes and impaired glucose tolerance (Chapter 65). The incident rate of type 2 diabetes is modestly higher among those with baseline depressive symptoms. Once type 2 diabetes was diagnosed, there was a positive association with depressive symptoms, illustrating the emotional burden of having diabetes [30]. The use of second-generation antipsychotic agents, commonly referred to as *atypical antipsychotics*, has been linked with hyperglycaemia and diabetes [31]. A complex association exists between mental illness, use of psychiatric medications, and diabetes [32].

Drug-induced metabolic changes

There is increasing recognition that some commonly used medications may be associated with adverse metabolic effects and increased risk of diabetes (Chapter 21) [33]. High-dose thiazide diuretics worsen insulin resistance and β-blockers can impair insulin secretion. The increasing use of highly active antiretroviral therapy (HAART) has dramatically reduced the mortality of people with human immunodeficiency virus (HIV) infection. However, protease inhibitors and, to a lesser extent, nucleoside reverse transcriptase inhibitors are associated with insulin resistance, deranged glucose and lipid metabolism, and an increased risk for type 2 diabetes. The growing use of such agents will likely have a significant impact on the epidemiology of diabetes in areas where HIV/AIDS is endemic, such as Africa [34].

Environmental toxins

Whereas most studies on the increasing burden of diabetes with a Westernized lifestyle have focused on changes in dietary patterns and increasingly sedentary behaviour, some studies suggest that environmental pollutants may represent a previously unrecognized link between urbanization and diabetes [35, 36]. For example, there is a strong cross-sectional association between serum concentrations of chlorinated persistent organic pollutants with diabetes [37] and also components of the metabolic syndrome [38]. Brominated flame retardants, bisphenol A, and perfluorinated compounds have emerged as other classes of organic pollutants that are associated with diabetes [39, 40]. These environmental toxins may accumulate in adipose tissue and act as endocrine disruptors, leading to dysregulation of glucose and lipid metabolism.

Low birth weight and fetal malnutrition

There is a relationship between the intrauterine environment, fetal malnutrition, and the risk of diabetes and cardiovascular disease later in life [41,42]. Maternal undernutrition and low infant birth weight, along with rapid postnatal growth, are associated with increased risk of diabetes in the offspring. This *mismatch* of a metabolic phenotype programmed during intrauterine development and the nutritionally rich postnatal environment may be most important in regions that are undergoing rapid economic development, and may be an important factor contributing to the rapid rise in diabetes in Asia and the Pacific region [43].

Maternal obesity, maternal hyperglycaemia, and other factors in early development

Offspring of women with obesity or women with diabetes have an increased risk of diabetes and cardiometabolic abnormalities [44,45]. This is partly caused by the effects of maternal overnutrition and of intrauterine hyperglycaemia on fetal growth, although it may also involve epigenetic changes [46]. With increasing numbers of women with obesity or young-onset diabetes, this is likely to exacerbate the epidemic of diabetes further by setting up a vicious cycle of diabetes begetting diabetes [42,47,48]. There is also increasing interest in the potential link between assisted reproduction technology and risk of diabetes and obesity in the offspring, though this remains an area of controversy, with limited and conflicting data [49].

Despite the increasing recognition of these novel risk factors, the main risk factors associated with diabetes remain the traditional ones such as increasing age, adiposity, physical inactivity, dietary factors, positive family history, and presence of other cardiometabolic risk factors, as outlined in Figure 5.1.

Methodological issues in the epidemiology of type 2 diabetes

In comparing epidemiological data in type 2 diabetes, one must be aware of the importance of the study methodology. Survey methods must be robust to allow comparison and standardization. A large, truly random sample of a community, with a good response rate,

is best; workplace samples may demonstrate *healthy worker* effects, whereas selective samples (e.g. volunteers or people with another disease) are the least useful because of inbuilt recruitment bias. The age distribution of sample populations is crucial in studying type 2 diabetes, whose prevalence rises with age; study populations must be age stratified and any comparisons age-adjusted, either within the dataset or standardized against a reference population. Finally, ascertainment methods are important, for example whether participants undergo an oral glucose tolerance test, with or without preliminary blood glucose screening. Although reference is often made to the global and national estimates of diabetes prevalence in the *IDF Diabetes Atlas*, one must be aware of several important limitations of these estimates. For countries in which prevalence studies are available, the data are presented in the *Atlas*. However, for many countries for which no updated prevalence studies are available, the estimates are based on modelled data from nearby countries matched in terms of percentage urbanization, ethnicity, and income group [50]. Owing to these methodological issues, prevalence figures for countries where estimates are based on modelling are not necessarily accurate, and not directly comparable with those from countries in which nationwide epidemiology surveys have been conducted, though these issues have been addressed to a certain extent in the latest version of the *Atlas* [1, 50].

Studies conducted in different regions of the world have highlighted an increase in the prevalence of type 2 diabetes. Although few would argue that this translates into an increasing burden associated with diabetes, it is important to recognize the factors that have contributed to this increased prevalence. Several factors directly affect the prevalence of diabetes and may partly account for the increasing prevalence (Figure 5.2). These include:

- Changes in the ratio of diagnosed to undiagnosed cases of diabetes.
- Population demographic changes with an ageing population.
- Earlier age at onset of diabetes.
- Longer survival in people with diabetes.
- Increasing incidence of diabetes [51].

The different factors may have different contributions depending on the population being studied, although most, if not all, are of some importance in most populations. The differences in the contributions of different factors to the prevalence of diabetes are illustrated by the fact that, for example, in Europe the incidence of diabetes has stabilized but longevity and higher case finding now explain the increased numbers, whereas in Africa and parts of Asia there is still an increase in incidence [1, 2, 43, 50].

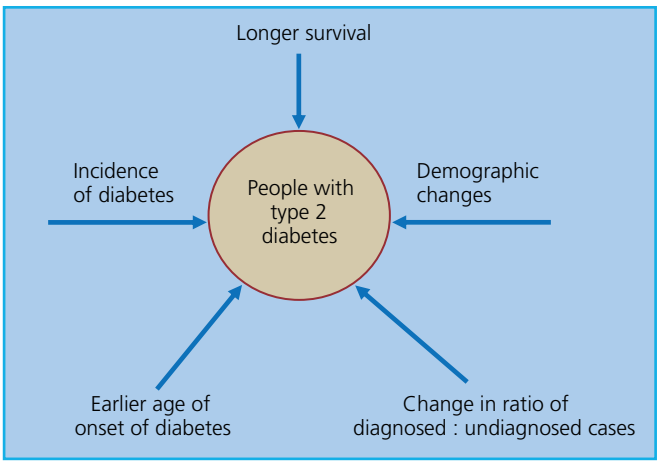

Figure 5.2 Diabetes epidemiological model. Factors directly affecting the prevalence of diabetes included in the present analysis. Source: Adapted from Colagiuri et al. 2005 [51].

Effects of changes in the definition of diabetes

Although it has long been established that diabetes is a condition associated with hyperglycaemia, there was no widespread accepted definition until the 1980s, when the World Health Organization (WHO) Expert Committee on Diabetes Mellitus defined diabetes as a state of chronic hyperglycaemia that may result from many environmental and genetic factors often acting together [52]. The precise degree of hyperglycaemia that defines diabetes has evolved with time and relies on epidemiological studies regarding the distribution of glucose levels within various populations.

There are several consequences of the changes in the definition of diabetes with time on the epidemiology of diabetes. First, the American Diabetes Association (ADA) and 1999 WHO classification lowered the diagnostic threshold of fasting glucose from 7.8 to 7.0 mmol/l, thereby increasing the number of individuals in any given population who fulfilled a diagnosis of diabetes mellitus.

It is important to appreciate whether the diagnosis was based on elevated fasting glucose or post-load values during an oral glucose tolerance test. Although the lower fasting glucose level of 7 mmol/l was chosen to resemble the diagnostic significance of the two-hour post-load concentration more closely, numerous studies have demonstrated that the fasting glucose and post-load criteria identify slightly different people in most populations [53–55]. The use of fasting glucose alone will reduce the overall prevalence of diabetes compared with that identified by two-hour post-load glucose values [56]. Furthermore, there is an increasing number of epidemiological studies that utilize the measurement of glycated haemoglobin (HbA_{1c}) as an indicator of dysglycaemia [57], and several professional organizations, including the ADA in 2010 and the WHO in 2011, have now included HbA_{1c} for the diagnosis of diabetes [4, 58], though this remains an area of debate [4, 58–60].

The WHO and ADA recommendations for the diagnostic criteria for diabetes and intermediate hyperglycaemia are summarized in Table 5.1. Although the lower ADA threshold for diagnosing impaired fasting glucose will result in more people being diagnosed with intermediate hyperglycaemia compared with the WHO recommendation, increased diagnostic activity, for example through the use of the oral glucose tolerance test, will increase the ratio of diagnosed to undiagnosed diabetes, and may have an impact on the prevalence rate reported in epidemiological studies. In a study utilizing 96 population-based cohorts to compare the different diagnostic criteria on population prevalence of diabetes, the prevalence based on HbA_{1c} was in general slightly lower than that based on fasting blood glucose. Furthermore, diabetes diagnosed on $HbA_{1c} \geq 6.5\%$ (48 mmol/mol) had a pooled sensitivity of ~53% (95% confidence interval [CI] 51.3–54.3%), compared with a definition of fasting glucose of ≥7.0 mmol/l for diagnosing individuals without a previous known history of diabetes [61].

In an earlier comprehensive report on the global prevalence of diabetes [62], the most important demographic change to diabetes prevalence across the world was the increase in the proportion of people aged >65 years. Another major factor that has affected the prevalence of diabetes is the increasing age-specific prevalence, especially in the younger age groups [62]. This suggests an earlier age of onset of diabetes, which may be of particular importance in developing countries. The tendency is for the prevalence of impaired glucose tolerance to decline as that of diabetes rises,

Table 5.1 Comparison of World Health Organization (WHO) and American Diabetes Association (ADA) recommendations for the diagnostic criteria for diabetes and intermediate hyperglycaemia.

	WHO (2006/2011)	ADA (2003/2010)
Diabetes		
Fasting plasma glucose	≥7.0 mmol/l (126 mg/dl) or	≥7.0 mmol/l (126 mg/dl)
2 h plasma glucose[a]	≥11.1 mmol/l (200 mg/dl)	
HbA_{1c}	(Since 2011) ≥6.5% (48 mmol/mol) (if assay standardized and accurately measured)	(Since 2010) ≥6.5% (48 mmol/mol) (if assay standardized and accurately measured)
Impaired glucose tolerance		
Fasting plasma glucose	<7.0 mmol/l (126 mg/dl) and	
2 h plasma glucose [a]	≥7.8 and <11.1 mmol/l (140 and 200 mg/dl)	
Impaired fasting glucose		
Fasting plasma glucose	6.1–6.9 mmol/l (110–125 mg/dl)	5.6–6.9 mmol/l (100–125 mg/dl)
2 h plasma glucose[a]	<7.8 mmol/l (140 mg/dl)	

[a]Venous plasma glucose 2 h after ingestion of 75 g oral glucose load.

suggesting that areas with a high ratio of impaired glucose tolerance to diabetes are at an earlier stage of the diabetes epidemic and thus may be a particular target for preventive strategies. Changes and variations in the ratio of impaired glucose tolerance to diabetes prevalence, the so-called *epidemicity index*, may provide a useful marker for the scale of the epidemic in that particular region [63].

Emerging data on the incidence of type 2 diabetes

While the prevalence of diabetes provides a good estimate of the total burden of diabetes in different parts of the world, diabetes prevalence can increase due to better care and longer survival of people with diabetes. Hence the incidence rate of diabetes is a better reflection of the risk of developing new-onset diabetes. However, data on the incidence of type 2 diabetes are comparatively limited. In a systematic review of studies reporting incidence of diabetes in adults between 1980 and 2017, it was noted that among the 47 studies included, the majority (66%) reported increases in diabetes incidence between 1990 and 2005, whereas the majority of studies between 2006 and 2014 noted stable or declining incidence [64]. In a more recent analysis of trends of incidence of diagnosed diabetes from different high- and middle-income settings, data from 22 million diabetes diagnoses from 19 high-income and 2 middle-income countries or regions suggest that the incidence of diagnosed diabetes may be stabilizing or declining in the high-income countries represented [65]. While this might be encouraging news, there is no room for complacency, as the rates of overweight and obesity continue to increase globally, and continued efforts to track and battle diabetes and its associated burden remain a major public health priority [1, 2, 50, 66].

Regional and ethnic patterns of type 2 diabetes worldwide

This section considers the geographical distribution and secular changes in the prevalence of type 2 diabetes and intermediate hyperglycaemia in the major regions of the world. Whenever possible, the most representative recent prevalence studies are presented. In addition, owing to a lack of recent prevalence studies, data from the *IDF Diabetes Atlas*, which utilized age- and sex-specific estimates for diabetes prevalence from available epidemiological surveys to extrapolate prevalence in related countries using a combination of criteria including geographical proximity, ethnic, and socioeconomic similarities, are also presented when necessary.

Current estimates of the total number of people with diabetes in each region of the world and in those countries with the highest overall numbers are shown in Figure 5.3. Table 5.2 shows the countries with the highest prevalence, and Table 5.3 lists the countries with the greatest number of people with diabetes. These estimates are based on modelling of data available from countries in which prevalence data were obtained from epidemiological surveys, and hence are only estimates that must be treated with caution [50].

Africa

Type 2 diabetes in the African continent provides contrasting pictures between more urbanized and more rural regions. Whereas poverty and malnutrition are still a major problem affecting sub-Saharan Africa, a region where diabetes is comparatively rare, urbanized areas such as North Africa are reporting increasing prevalence rates [66]. The IDF estimated that overall, ~4.5% of the adult population in the African region are currently affected by diabetes and this is projected to increase to 5.2% by 2045 [2]. Other important epidemiological issues in the region include a low incidence of type 1 diabetes, except in Eastern Africa, where rates of type 1 diabetes are comparatively high. There is also the occurrence of atypical *ketosis-prone* diabetes. This initially presents as type 1 diabetes with severe hyperglycaemia and ketosis, but subsequently has long-term remission with a clinical course more compatible with type 2 diabetes [67]. In addition, there is also a form of early-onset diabetes termed malnutrition-related diabetes mellitus that is associated with past or present malnutrition and sometimes accompanied by pancreatic calcification [34]. Although infective diseases such as HIV infection and tuberculosis are currently the main causes of mortality in sub-Saharan Africa, the increasing prevalence of diabetes and other non-communicable diseases is likely to overtake infections as major causes of mortality.

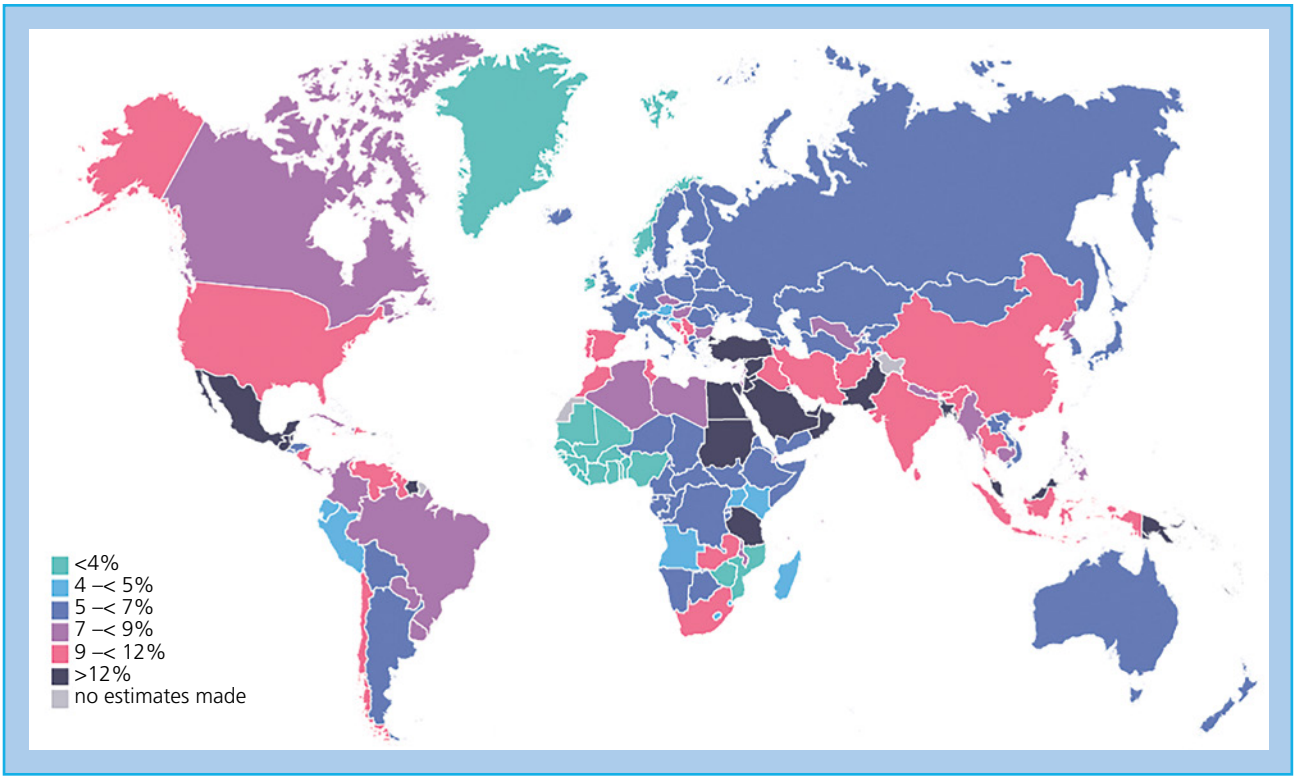

Figure 5.3 Global prevalence of diabetes. Source: Adapted from *IDF Diabetes Atlas* 2021 [2].

Table 5.2 List of countries with the highest prevalence of diabetes (age group 20–79 years, age-adjusted for comparative prevalence) in 2021.

Rank	Country	Prevalence (%)
1	Pakistan	30.8
2	French Polynesia	25.2
3	Kuwait	24.9
4	New Caledonia	23.4
5	Northern Mariana Islands	23.4
6	Nauru	23.4
7	Marshall Islands	23.0
8	Mauritius	22.6
9	Kiribati	22.1
10	Egypt	20.9

Source: Data from *IDF Diabetes Atlas* 2021 [2], Chapter 3, Table 3.5.

Table 5.3 Top 10 countries with the greatest number of people with diabetes (age range 20–79 years) in 2021.

Rank	Country	Persons (millions)
1	China	140.9
2	India	74.2
3	Pakistan	33.0
4	USA	32.2
5	Indonesia	19.5
6	Brazil	15.7
7	Mexico	14.1
8	Bangladesh	13.1
9	Japan	11.0
10	Egypt	10.1

Source: Data from *IDF Diabetes Atlas* 2021 [2], Chapter 3, Table 3.4.

In sub-Saharan Africa, only a small proportion of the population reaches ages at which type 2 diabetes becomes a major health problem. Although greater access to highly active antiretroviral therapy (HAART) has led to markedly reduced mortality, the improvement in life expectancy, coupled with the adverse metabolic effects of HAART, is likely to contribute to further increases in the prevalence of type 2 diabetes within the region [34, 68].

Sub-Saharan Africa

There is a relative paucity of prevalence data from sub-Saharan Africa, with most of the studies coming from Ghana, Cameroon, Nigeria, Tanzania, and South Africa [67, 69]. In a systematic review of prevalence data from Ghanaians and Nigerians, diabetes was rare at 0.2% in urban Ghana in 1963 and 1.65% in urban Nigeria in 1985. The prevalence of diabetes had risen to 6.8% in Nigeria in 2000 (for adults aged ≥40 years) and 6.3% in Ghana in 1998 (for adults aged ≥25 years) [70, 71]. In Cameroon (West Africa), adults aged 24–74 years had an overall diabetes prevalence of 1.1%, with an impaired glucose tolerance rate of 2.7%. Prevalence rates in the capital of Cameroon (Yaounde) were 1.3% for diabetes and 1.8% for impaired glucose tolerance, compared with rural prevalences of 0.8% for diabetes and 3.9% for impaired glucose tolerance [72]. Undiagnosed cases accounted for most cases in these studies, again reflecting a region in the early stages of a looming diabetes epidemic. In a recent systematic review of 41 studies of the prevalence

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of diabetes among older adults on the African continent, overall prevalence was substantially higher at 13.7% among adults aged 55 or older, and was higher among studies using the oral glucose tolerance test (OGTT) than fasting glucose, and higher in urban versus rural settings [73].

In South Africa, both diabetes and impaired glucose tolerance are commoner in both urban and rural communities. In Cape Town, age-adjusted prevalence was 8% for diabetes and 7% for impaired glucose tolerance [74]. A study conducted in a rural South African community based on a 75 g OGTT and the 1998 WHO criteria reported overall age-adjusted prevalence of diabetes of 3.9%, impaired glucose tolerance of 4.8%, and impaired fasting glycaemia of 1.5%. Notably, 85% of the cases with diabetes were uncovered by the survey [75]. In addition to exposure to an urban environment, other factors that determine the risk of type 2 diabetes in African populations include positive family history, ethnic origin, central adiposity, and physical inactivity [76]. Possible ethnic differences have been examined in several studies. In both Tanzania and South Africa, migrant Asians have higher diabetes prevalence rates than Indigenous Africans [77], but this could reflect lifestyle differences. In Tanzania the difference was particularly marked (1.1% in Africans vs 9.1% in Asians), which again emphasizes the low prevalence in urban East Africans. In a recent systematic review including 11 studies of the prevalence of type 2 diabetes in South Africa published between January 1997 and June 2020, the pooled prevalence in adults aged 25 or above was 15.25% (95% CI 11.07–19.95%) for type 2 diabetes, 9.59% (5.82–14.17%) for impaired glucose tolerance, 3.55% (0.38–9.61%) for impaired fasting glycaemia, and 8.29% (4.97–12.34%) for newly diagnosed type 2 diabetes [78].

The emerging epidemic of type 2 diabetes is further compounded by the various problems hampering the delivery of effective diabetes care within this region. This has resulted in poor glycaemic management among most people with diabetes, and also a high frequency of chronic microvascular complications. The rising prevalence of diabetes may also hamper tuberculosis control efforts by increasing the number of susceptible individuals in endemic areas [74]. Better access to healthcare and treatment, improvements in infrastructure to support services (for example, by aligning diabetes care with screening and healthcare delivery for infectious diseases such as HIV and tuberculosis) and healthcare information systems, and also primary prevention measures are urgently needed to reduce the burden of acute and chronic complications of diabetes in the region [34, 67, 68, 79, 80].

North America

Diabetes and its complications are common and a significant cause of morbidity in North America. The NHANES reported a crude prevalence of total diabetes in 1999–2002 of 9.3%, comprising 6.5% diagnosed and 2.8% undiagnosed [81]. This was significantly increased compared with a crude prevalence of total diabetes of 5.1% in 1988–1994, mainly through an increase in diagnosed diabetes. There was a marked variation in prevalence between ethnic groups, with age- and sex-standardized prevalence of diagnosed diabetes approximately twice as high in non-Hispanic Black Americans (11%) and Mexican Americans (10.4%) compared with non-Hispanic white Americans (5.2%). The prevalence of diabetes among older people of these minority groups was particularly high, exceeding 30% [81].

The high prevalence rates in US Hispanic people and Black Americans are well documented. In 1991, the age-adjusted prevalence of diabetes was 6% in white Americans, 9% in Cubans, 10% in Black Americans, 13% in Mexican Americans, and 13% in Puerto Ricans [82]. Rates have risen in all groups, but these differences appear to persist. Between 1987 and 1996, the 7–8-year incidence of type 2 diabetes approximately tripled in both Mexican Americans and non-Hispanic white Americans, although the absolute rate was twice as high in the Mexican Americans [83]. Type 2 diabetes is also significantly commoner among older Puerto Ricans (38%) and Dominicans (35%) than among non-Hispanic white Americans (23%) [84]. Economic disadvantage may explain much of the excess prevalence of type 2 diabetes among African American women [85].

Other populations in the USA that are particularly at risk of type 2 diabetes are the Indigenous communities, notably the Pima, of whom 50% have diabetes [86]. Reports have highlighted the developing epidemic of type 2 diabetes in Indigenous American youth [87]. Among 15–19-year-olds, diabetes affected 5.1% of Pima (a sixfold increase in prevalence over the previous 20 years) and 0.2% of Canadian Cree and Ojibway. The overall prevalence among all US Indigenous peoples of this age is 0.5%. This epidemic of type 2 diabetes in young Indigenous Americans is supported by secular trends in the incidence rate of type 2 diabetes over the previous 40 years in Pima, which showed a more than fivefold increase in incidence rates among Pima aged 5–14 years [88].

A similar situation was seen in Canada, where Indigenous peoples had more than a twofold increase in prevalence compared with the general population [89]. Other minority groups are also not spared. Among native Hawaiians (Polynesians), the crude (i.e. not age-adjusted) prevalence rates of type 2 diabetes and impaired glucose tolerance were reported in 1998 to be 20% and 16%, respectively. The age-adjusted rate for type 2 diabetes was four times higher than among the US NHANES II study population [90]. In 1991, second-generation Japanese Americans had prevalence rates of 16% (diabetes) and 40% (impaired glucose tolerance) [91], and incidence rates remained high at 17.2 per 1000 person-years [92]. This may be due to the increase in visceral adiposity in a population predisposed to impaired β-cell function [93]. Other Asian populations living in the USA that are particularly prone to diabetes include Asian Americans, in whom linguistic difficulties may be a particularly relevant barrier to diabetes education and effective care delivery [94].

It has been estimated that the number of adults in the USA with diagnosed diabetes will rise from 11 million in 2000 (overall prevalence 4.0%) to 29 million in 2050 (overall prevalence 7.2%). The fastest growth is expected to be among Black Americans. The projected increase of 18 million is accounted for by approximately similar contributions from changes in demographic composition, population growth, and secular trends [95]. In 2021 it was estimated that 32.2 million people in the USA had diabetes, of whom 4.0 million were undiagnosed [2]. The US Centres for Disease Control and Prevention (CDC) reported a crude prevalence of total diabetes in 2018 of 13.0%, comprising 10.2% diagnosed and 2.8% undiagnosed [96]. The direct and indirect medical cost attributed to diabetes in the USA in 2017 was $327 billion [97]. The percentage of diagnosed people reaching glycaemic goals and achieving risk factor control has improved over the last two decades, although only 14% met all three targets regarding glycaemic, blood pressure, and lipid management, along with smoking cessation [98]. There has been a substantial reduction in the rates of diabetes-related complications over the last two decades, especially regarding myocardial infarction and acute hyperglycaemic emergencies [99].

An increasing number of younger people will be affected. In the SEARCH for Diabetes in Youth Study, a multiethnic, population-based study, the incidence of diabetes was 24.3 per 100 000 person-years. The incidence rates of type 2 diabetes were highest among Indigenous Americans and African American adolescents, varying from 17 to 49.4 per 100 000 person-years, compared with 5.6 per 100 000 person-years in non-Hispanic white Americans [100].

Caribbean

Studies in Jamaica exemplify the secular trend in the West Indies. Rates in the 1960s (underestimated owing to the screening procedure used) [101] were low, but rose in the 1970s to 4% in those aged 25–44 years and 8–10% in those aged 45–64 years [102, 103], and to an overall rate of 7.4% in 1996 [104]. A report in 1999 indicated prevalence rates of 16% in women and 10% in men (13% overall). As elsewhere, this exceeds the rate of rise among European-origin populations and parallels the spread of obesity [105].

Central and South America

Data from this region are scarce. In the Indigenous Mapuche in rural Chile, the prevalence of type 2 diabetes estimated in 2001 was 3% in men and 5% in women [106], which represents a substantial rise above the very low prevalence of <1% reported in 1985 [107]. Diabetes is clearly much more common in urban communities, for example 14% in Mexico City in 1994 [108], compared with a 5–10% prevalence nationwide [109]. Surveys in Brazil and Colombia in the early 1990s indicated age-adjusted prevalence rates of ~7% [110, 111]. A study in Brazil revealed a rate of self-reported diabetes of 10.1% [112]. A systematic review and meta-analysis of prevalence studies between 1980 and 2015 noted an increase in prevalence over the last three decades, from 7.4% (95% CI 7.1–7.7%) in the 1980s to 15.7% (9.8–24.3%) in the 2010s [113]. A high prevalence of abdominal obesity was noted in these populations, affecting more than 80% of women [109].

Europe

This region contains a diverse mix of countries that have marked differences in affluence and includes some of the most developed countries in the world. Nevertheless, updated nationwide survey data are only available in some countries. In the *IDF Diabetes Atlas*, data sources were available for 39 of the 59 European countries and territories, including recent data from the last five years for 14 countries [2]. National prevalence of diabetes ranged from 4.0% in Ireland to 15.9% in Turkey [2, 50] (Table 5.4).

Table 5.4 National estimates of diabetes in Europe in 2021.

	Prevalence of diabetes (%)	
Country	National population[a]	Comparative population[b]
Albania	11.5	9.1
Austria	6.6	4.6
Belgium	4.9	3.6
Cyprus	9.7	8.6
Denmark	7.3	5.3
Finland	9.7	6.1
France	8.6	5.3
Germany	10.0	6.9
Greece	9.6	6.4
Iceland	8.3	5.5
Ireland	4.0	3.0
Israel	9.9	8.5
Italy	9.9	6.4
Malta	11.2	8.0
The Netherlands	6.8	4.5
Norway	4.8	3.6
Poland	9.4	6.8
Spain	14.8	10.3
Sweden	6.8	5.0
Turkey	15.9	14.5
UK	8.2	6.3

[a] Prevalence based on current age/sex composition.
[b] Prevalence standardized to global age/sex composition.
Source: Data from *IDF Diabetes Atlas* 2021 [2], Appendix.

United Kingdom

Type 2 diabetes imposes particular burdens on inner cities with multiethnic populations, as those originating from the Indian subcontinent have a high diabetes prevalence. In typical studies [114, 115], the age-adjusted prevalence rates were 3% and 5% in white European men and women, respectively, compared with 12% and 11% in their Asian counterparts in the UK. Asians also show a higher prevalence of impaired glucose tolerance, a male preponderance, a younger age at diagnosis, and a lower proportion of undiagnosed diabetes [115].

Poverty and social deprivation apparently contribute to the increasing prevalence of type 2 diabetes among inner-city residents: for example, in all ethnic groups in inner-city Manchester there was a surprisingly high age-standardized prevalence, including a rate of 20% among white Europeans [116]. Social deprivation, obesity, physical inactivity, and smoking tend to co-segregate, which may explain this phenomenon. The importance of dietary factors was highlighted by two studies, which demonstrated an association between high dietary energy density or unhealthy dietary patterns (characterized by a high intake of sugar-sweetened beverages, burgers and sausages, and snacks) and incident type 2 diabetes [117, 118]. In the Ely Study, a population-based longitudinal study, the 10-year cumulative incidence of diabetes was 7.3 per 1000 person-years [119]. It has been estimated that the UK National Health Service spends at least £10 billion a year on diabetes, equivalent to ~10% of its budget, with 80% of this being spent on treating complications of diabetes [120].

Scandinavia and Nordic Countries

Here, the more homogenous population may indicate more accurately the true prevalence of type 2 diabetes among white Europeans. A survey in northern Sweden revealed a prevalence of diabetes of 8.1% in 2002 [121]. Similar data were obtained in a study in Finland, with the age-standardized prevalence of diabetes in 45–64-year-olds being 10.2% for men and 7.4% for women [122]. Lower prevalence data were noted for Iceland [123].

In the early 1990s type 2 diabetes was rare in northern Finland, but the prevalence of impaired glucose tolerance was 29% in men and 27% in women [124], comparable to that in a homogenous white female Swedish population aged 55–57 years (28%) [125]. In Denmark, ~15% of the population had impaired glucose tolerance in 2003 [126]. The high prevalence of impaired glucose tolerance in Finland prompted the Finnish Diabetes Prevention Study [127], which examined whether lifestyle changes could prevent the development of type 2 diabetes. Strikingly, nutritional advice and

increased physical activity reduced the risk of developing diabetes by 58% in people with impaired glucose tolerance, and the effect was sustained over subsequent follow-up [127]. A more recent study in three regions in Finland noted prevalence of impaired glucose tolerance of 10.5% and 9.2% in men and women, respectively, substantially lower than previously reported figures from northern Finland. It is unclear whether this difference is due to regional differences or to changes in the diabetes-to-impaired glucose tolerance ratio [122].

Using a register of people with diabetes, the calculated incidence rate of diabetes in Denmark was 1.8 per 100 000 at age 40 years and 10 per 100 000 at age 70 years. The incidence rate increased by 5% per year before 2004, but then stabilized. The lifetime risk of diabetes was estimated at 30% [128]. Another study in Finland noted an alarming increase in the incidence of type 2 diabetes among young adults, with the age-adjusted incidence of type 2 diabetes among 15–39-year-olds being 11.8 per 100 000 per year. The incidence rate increased by 7.9% per year. Interestingly, despite the country having the highest incidence of childhood type 1 diabetes in the world, the incidence of type 2 diabetes among young adults in Finland is approaching that of type 1 diabetes among the 15–39-year-old age group (age-adjusted incidence of type 1 diabetes 15.9 per 100 000 per year) [129].

Continental Europe

A population-based survey in Verona, Italy, revealed an overall prevalence of type 2 diabetes of 2.5%, which increased significantly after the age of 35 years [130]. In northern Italy, the age-adjusted prevalence of type 2 diabetes was 9% in men and 8% in women over the age of 44 years [131]. In a study that compared the prevalence of diabetes in Casale Monferrato in northwest Italy in 1988 and 2000, the age- and sex-adjusted prevalence of diabetes had increased from 2.1% in 1988 to 3.1% in 2000, with higher age-specific prevalence rates of diabetes in every age group in the later survey, including a twofold increase in the risk for those aged ≥80 years [132].

In France, the MONICA study estimated the adjusted prevalence of type 2 diabetes to be 7% in men and 5% in women aged 35–65 years and the adjusted prevalence of impaired fasting glucose to be 12% in men and 5% in women [133]. The prevalence of diabetes increased to 19% in men and 9% in women aged over 60 years [134]. In the more recent French Nutrition and Health Survey conducted between 2006 and 2007, the prevalence of diabetes according to elevated fasting plasma glucose or HbA_{1c} ≥6.5% (48 mmol/mol) was 5.6%, with undiagnosed diabetes contributing to fewer than 20% of all cases of diabetes [135].

In the Netherlands, type 2 diabetes affects 8% of older white Dutch [136]; 65% of those with impaired fasting and post-load glucose levels went on to develop diabetes within six years [137]. In a prospective population-based study between 1998 and 2000, the age- and sex-adjusted prevalence of diagnosed diabetes was 2.2% at baseline and 2.9% after two years of follow-up, with people aged ≥70 years accounting for 50% of the population with type 2 diabetes [138].

In Greece, the prevalence of diabetes increased from 2.4% in 1974 to 3.1% in 1990 [139], as the population aged and obesity became more widespread [140, 141]. The prevalence of type 2 diabetes was 7.6% in men and 5.9% in women in a survey conducted between 2001 and 2002 [142]. In a follow-up study on those free of cardiovascular disease at baseline, the incidence rate of diabetes within a five-year period was 5.5% [143]. In Turkey, the overall prevalence rates of type 2 diabetes and impaired glucose tolerance were 6% and 9%, respectively. Low levels of occupational activity, family history, and obesity were all associated risk factors [144, 145]. Adherence to a Mediterranean diet may have protective effects against diabetes [146].

Prevalence data from eastern Europe are comparatively sparse. The age-adjusted prevalence of type 2 diabetes for men and women in Fergana, Uzbekistan, was estimated to be 8% in both urban men and women, with impaired glucose tolerance affecting 5% of men and 6% of women. Lower prevalence rates for both type 2 diabetes and impaired glucose tolerance were reported for semirural inhabitants [147]. A survey in a rural area in the Sirdaria province of Uzbekistan confirmed similar age-adjusted prevalence rates of diabetes for men (10%) and women (7.5%). However, prevalence rates of impaired glucose tolerance in Sirdaria women (14%) and men (11%) were higher than for semiurban or urban inhabitants in Fergana [148]. In Russia, the estimated prevalence was 6% in men and 7% in women for diabetes and 6% and 13%, respectively, for impaired glucose tolerance; clustering of hyperlipidaemia, obesity, hypertension, and low 10-year survival was observed among those with diabetes [149]. A survey conducted in Moscow found a low incidence of reported diagnoses of diabetes (2%) [150], which was supported by another study based on self-reported doctor diagnoses [151]. In addition to underdiagnosis, undertreatment and infrequent insulin use are also likely to contribute to the burden of morbidity [151]. Many of the estimated prevalence data in other eastern European countries have been extrapolated from data from Poland, where the prevalence of type 2 diabetes increased from 3.7% to 10.8% between 1986 and 2000, with a similar increase in prevalence of impaired glucose tolerance from 2.9% to 14.5% [152].

South-East Asia

India

India is the second most populous country in the world and also second in terms of the number of people with diabetes, with ~69.2 million affected in 2015, a figure that is projected to rise to 123.5 million by 2040 [2]. Sequential surveys in India [153–156] indicate that the prevalence of diabetes has risen steadily since the 1970s, although methodological differences hamper direct comparisons between prevalence studies.

The National Urban Diabetes Survey, carried out in six cities in 2001, found age-standardized prevalence rates of 12% for diabetes (with a slight male preponderance) and 14% for impaired glucose tolerance; people ≤40 years old had prevalence rates of 5% (diabetes) and 13% (impaired glucose tolerance) [156]. Diabetes was positively and independently associated with increasing age, BMI, and waist/hip ratio, and a family history of diabetes, impaired glucose tolerance, higher monthly income, and physical inactivity. Impaired glucose tolerance showed associations with age, BMI, and family history of diabetes. Subsequent studies showed an increasing prevalence, with a prevalence rate of 14.3% reported in the Chennai Urban Rural Epidemiology Study (CURES-17) [157] and 18.6% in the city of Chennai in another study [158]. In the large Indian Council of Medical Research-INdiaDIABetes (ICMR-INDIAB) study involving >13 000 adults across 188 urban and 175 rural sites in four different regions, the prevalence of diabetes was 10.4% in Tamil Nādu, 8.4% in Maharashtra, 5.3% in Jharkhand, and 13.6% in Chandigarh [159]. This gave rise to estimates of 62.4 million people with diabetes and 77.2 million people with pre-diabetes in India in 2011 [152]. In addition to the

increasing prevalence of diabetes, there appears to be a decreasing prevalence of impaired glucose tolerance [157]. Another secular trend is the shift towards younger onset of diabetes, especially in urban areas, where up to 36% of those with diabetes are aged ≤44 years [157, 158].

Urban–rural differences in the prevalence of diabetes have been consistently reported in different studies in India. A study in Chennai noted a progressive increase in prevalence rate with increasing urbanization: 2.4% in rural areas, 5.9% in semiurban areas, and up to 11.6% in urban areas [155, 160]. Likewise, more recent data revealed a prevalence of 18.6% in the city of Chennai compared with 16.4% in a town, and 9.2% in peri-urban villages [158]. In a study of 77 centres in India (40 urban and 37 rural), the standardized prevalence rate for diabetes in the total Indian, urban, and rural populations was 4.3%, 5.9%, and 2.7%, respectively. Although the prevalence rates of diabetes and impaired glucose tolerance are significantly higher in urban than rural areas, it appears that the rural–urban gradient is becoming increasingly attenuated [161]. In a recent nationwide cross-sectional study of 15 states in India, overall prevalence of diabetes was 7.3% (95% CI 7.0–7.5%), with 47.3% being undiagnosed. A further 10.3% (95% CI 10.0–10.6%) had pre-diabetes, with both diabetes and pre-diabetes showing large differences in prevalence between the different states [162].

The Chennai Population Study (CUPS) in 2008 reported alarming rates of incident diabetes (20.2 cases per 1000 person-years) [163]. This has been confirmed by a recent study, which reported an incidence of 22.2 per 1000 person-years, where 59% of those with pre-diabetes progressed to diabetes during a mean follow-up of 9.1 years [164]. Identification of those at high risk and increasing the awareness of the population are much needed. A risk score specific for the Indian population, the Indian Diabetes Risk Score (IDRS), has been developed. It utilizes four clinical variables: age, family history, regular exercise, and waist circumference. A score of >21 identifies those with diabetes with a sensitivity and specificity of close to 60% [165]. This will help target high-risk individuals for early intervention, since lifestyle modification is effective in reducing the progression from impaired glucose tolerance to diabetes in the Indian population [166]. The pilot phase of a National Programme on Diabetes, Cardiovascular Disease, and Stroke (NPCDS) was launched by the Ministry of Health and Family Welfare in 2008, with the aims of improving awareness of lifestyle-related diseases, disease prevention through screening and targeted intervention, and coordinating the multisector effort that is urgently needed to address the epidemic of obesity and diabetes in India [167].

Pakistan, Bangladesh, and Sri Lanka

The situation in these countries largely mirrors that in India. Diabetes is particularly common (16% of men, 12% of women) in the rural Sindh province in northern Pakistan [168]. A more recent study in Pakistan indicated similar prevalence rates of 10–11% in urban and rural men and urban women, although lower rates were seen in rural women (5%). However, impaired glucose tolerance rates in women were twice those in men [169]. Combining the data from the four provinces of Pakistan, the prevalence of diabetes in the urban areas was 6.0% in men and 3.5% in women, with a total of 22% of the urban population estimated to have some degree of glucose intolerance [170]. In rural Bangladesh, diabetes prevalence was reported in an older study to be 2.1% compared with an impaired glucose tolerance prevalence of 13%, despite a mean BMI of only 20.4 kg/m^2 [171]. A recent study based on fasting glucose criteria alone that included >7000 adults reported a prevalence of 9.7% [172].

In addition to urbanization, the main factor for the high prevalence of diabetes and metabolic abnormalities among Asians is the tendency for central obesity and insulin resistance [9, 155, 173–175]. Despite being born smaller, with a lower birth weight, Indian babies have more body fat, which persists into adulthood, thus putting them at increased risk of cardiometabolic complications [176]. Interestingly, one study showed that maternal nutrition and, in particular, low maternal vitamin B_{12} and high folate might be associated with increased adiposity and risk of type 2 diabetes in the offspring [177], suggesting that in addition to increased intake of fat and calorie-rich foodstuffs, other dietary factors may play a contributory role.

Mauritius

The high prevalence of diabetes and cardiovascular disease on the island of Mauritius, in the Indian Ocean, has been intensively studied. Here, diabetes is common in an urbanized setting: across several ethnic groups (Asian Indian, Chinese, and Creole) in 1990 the prevalence rates were 10–13%, rising to 20–30% in those aged 45–74 years [178]. A repeat survey in 1998 revealed a rise in prevalence of type 2 diabetes to 17.9%. In both studies, the highest prevalence was seen in Asian Indians [178, 179]. The age-standardized prevalence of diabetes in 2009 was 22.3% among men and 20.2% among women, representing an increase of over 60% compared with figures from 1987 [180].

Middle East

Marked socioeconomic changes in many countries in the region, especially among the affluent oil-producing countries, have led to dramatic changes in lifestyle, with changes in nutritional intake, decreased physical activity, and increased obesity and smoking. This, coupled with increasing urbanization and improved life expectancy, has led to a marked increase in the prevalence of diabetes and impaired glucose tolerance (Table 5.5). A recent review of the prevalence of diabetes in the Middle East highlighted the paucity of data and large differences in prevalence rates among different countries. Obesity and age appeared to be the main drivers of high prevalence [193]. Saudi Arabia, Kuwait, and Qatar are among the countries with the highest prevalence rates of diabetes [2], highlighting this region as one that requires concerted public health action to reduce the potential impact of diabetes [194].

North Africa

Egypt is among the top 10 countries with the highest burden of people with diabetes [2]. Prevalence rates are also relatively high (3–8%) in Sudan and Tunisia. An Egyptian study of adults aged >20 years showed an impaired glucose tolerance prevalence rate of 10% [195]. Urban–rural differences were demonstrated: in Cairo city diabetes was more common (prevalence 14–20%, depending on socioeconomic status), whereas the impaired glucose tolerance prevalence was lower (6–9%). The converse applied in a rural setting, with a diabetes prevalence of only 5% but a higher impaired glucose tolerance prevalence of 13%. This may reflect the diabetes epidemic being at an earlier stage in rural populations. In the Tunisian National Nutrition Survey, the prevalence of diabetes was 9.9%, giving an age-adjusted prevalence of 8.5%, with marked urban–rural differences [196].

Table 5.5 Prevalence of diabetes from reported epidemiology studies in selected countries in the Middle East.

Year	Country [Reference]	Prevalence (%)	
		Type 2 diabetes	Impaired glucose tolerance
1998	Lebanon [181]	13.2	6.0
2006	Oman [182]		
	Men	11.8	
	Women	11.3	
2000	Oman [183]		
	Men	11.8	7.1 (IFG)
	Women	11.6	5.1 (IFG)
1995	Oman [184]		
	Men	9.7	8.1
	Women	9.8	12.9
2011	Saudi Arabia [185]		
	Men	34.7	
	Women	28.6	
2000	Saudi Arabia [186]		
	Men	26.2	14.4
	Women	21.5	13.9
1995	Saudi Arabia [187]		
	Men	11.8	10.0
	Women	12.8	9.0
1992	Iran [188]		
	Urban men	7.1	8.9
	Urban women	7.6	14.9
	Rural	7.3	7.2
2014	Iraq [189]		
	Men	19.6	29.1
	Women	19.8	
2014	Kuwait [190]		
	Men	20.4	
	Women	17.4	
2004	Jordan [191]	17.1	7.8
2009	Qatar [192]	16.7	
	Men	15.2	
	Women	18.1	

IFG, Impaired fasting glycaemia.

Western Pacific region

Australia

The first report of the AusDiab Study [197], published in 2000, provides information about diabetes in a high-income country. The overall prevalence of diabetes in Australians aged ≥25 years was 7.5% (8% for men and 7% for women), rising from 2.5% in those aged 25–44 years to 24% among those aged ≥75 years; the prevalence had more than doubled since 1981 [198, 199]. Around 50% of cases discovered in this survey were previously undiagnosed. The combined prevalence of impaired fasting glucose and impaired glucose tolerance was 16% (men 17%, women 15%); hence almost 25% of Australians aged ≥25 years have abnormal glucose metabolism. In Australia, type 2 diabetes accounts for over 85% of cases and type 1 diabetes for 10%. Using data from the AusDiab study, it has been estimated that the prevalence of diabetes is likely to rise from 7.6% in 2000 to 11.4% by 2025 [200]. In the 2012 AusDiab Study Report, the annual incidence of diabetes was reported to be 0.8% per year for men and 0.6% per year for women [201].

Type 2 diabetes is commoner in Indigenous Australian populations, for example 16–30% of adults in the Aboriginal and Torres Strait Islander communities [202]. In this population, diabetes was associated with higher rates of hypertension (69% vs 21%), obesity (44% vs 16%), elevated triglyceride, and lower HDL cholesterol concentrations compared with those who have normal glucose tolerance.

New Zealand

In New Zealand, type 2 diabetes is consistently commoner among Polynesians (Māoris and Pacific Islanders) than in white New Zealanders: it accounts for 89% of diabetes in white New Zealanders and 95% in Polynesians. Polynesians are also diagnosed, on average, 5–10 years younger than white New Zealanders and have a four- to eightfold higher prevalence of diabetic nephropathy. Strikingly high prevalence rates of diabetic nephropathy of 37–75% were reported for unemployed men, emphasizing again the role of socioeconomic status [203]. In the 2006–2007 New Zealand Health Survey, prevalence rates reported for adults aged >30 years were 4.3% for white New Zealanders, 5.8% for Māoris, 6.5% for Asians, and 10.0% for Pacific Islanders [204, 205].

Pacific Island countries

The Melanesian, Micronesian, and Polynesian populations of the Pacific Islands show great variations in diabetes prevalence, largely attributable to differences in economic development and lifestyle. Some of the highest prevalence rates worldwide come from this region, notably from Nauru and Papua New Guinea. The Micronesian population of Nauru, made wealthy by bauxite mining and with a longer history of Westernization than other Pacific Island countries, currently has an age-standardized prevalence rate of 40%. High prevalence rates in Nauru have been maintained since the late 1970s, but now appear to have stabilized as bauxite mining is exhausted [43, 206].

Fiji has a largely biethnic population consisting of native Fijians of Melanesian ancestry together with migrants from India. Recent surveys from Fiji are lacking, but a survey conducted over 30 years ago showed that diabetes prevalence rates were already higher among Indian migrants than in Melanesians. In adults above 20 years of age, crude prevalence rates were 13% among Indian migrants (with no significant urban–rural gradient), but 7% and 1.7% among urban and rural Melanesians, respectively [207]. At the time, these results were thought to indicate a difference in ethnic (genetic) predisposition, but this conclusion has since been tempered by the finding of high prevalence rates in urbanized Melanesians in Papua New Guinea.

The situation in Papua New Guinea provides an excellent example of the damage inflicted by rapid urbanization: diabetes is virtually non-existent in highland populations [208], in stark contrast to the age-standardized prevalence rate of over 40% among urbanized Koki people (Melanesians) in Port Moresby [209]. Intermediate rates are reported in Austronesians of coastal ancestry.

High prevalence rates of diabetes have been reported in Polynesian populations, conspicuously associated with obesity, both conditions being particularly common in Polynesian women. In Western Samoa, diabetes prevalence was reported in 1991 to be 7–9% in two rural communities and 16% in Apia; the prevalence had doubled since 1978 [210]. In the Kingdom of Tonga, situated south of Samoa, the age-standardized prevalence of diabetes was 15.1%, of which 80% was undiagnosed [211].

Diabetes remains undiagnosed in most Pacific Island people with the disease, perhaps 80–100% in some communities, compared with around 25–50% in high-income countries [199]. This is likely to contribute to high rates of complications and frequent presentation with diabetes-related problems, such as foot sepsis [212].

Japan

Type 2 diabetes has become commoner in Japan since the 1960s, and data from rural parts of the country suggested a prevalence of 9.1% in men and 10.8% in women, with corresponding impaired glucose tolerance prevalence rates of 12% and 16.5% for Japanese men and women, respectively [213]. A National Diabetes Survey conducted in 2002 estimated a prevalence of 9% [214]. In the National Health and Nutrition Survey in 2007, it was estimated (using HbA_{1c}) that the prevalence of diabetes was 15.3% in men and 7.3% in women [215]. The emerging problem of type 2 diabetes among Japanese children is now recognized as a critical problem in that country. Type 2 diabetes cases outnumber type 1 diabetes in children and adolescents by a ratio of 4 : 1 [216], and the incidence rate of type 2 diabetes for 1981–1990 was 4.1 per 100 000 person-years, approximately twice the incidence rate of type 1 diabetes [217]. Nutritional factors are believed to play an important part, with the prevalence of diabetes among Japanese Americans approximately twice that among Japanese in Japan [218].

The causes of death in people with type 2 diabetes have also shifted, possibly because of Westernization of diet and increased fat and total calorie intake; higher death rates from renal disease than in white European populations are now being supplanted by rising deaths from coronary artery disease [219]. To reduce the burden of diabetes, the Japanese government has launched a large national strategic research project named J-DOIT to reduce diabetes, improve follow-up, and reduce complications of diabetes [220].

Korea

In the Korean National Health and Nutrition Survey conducted in 2001, the age-adjusted prevalence of diabetes was reported to be 7.6%. The prevalence of impaired fasting glucose was an alarming 23.9% [221], suggesting a future epidemic of diabetes in the Korean population, similar to that in other Asian countries [222]. In the Korean National Health and Nutrition Survey conducted in 2010–2012, the prevalence of diabetes was reported to be 10.1% [223].

China and Chinese populations

The rapid increase in the prevalence of type 2 diabetes in China provides one of the most striking examples of the impact of urbanization on increasing diabetes prevalence. China, with its current population of nearly 1.4 billion, is the world's most populous country. Diabetes used to be rare: prevalence rates reported between 1980 and 1990 were consistently ≤1.5% even in urban areas such as Shanghai [224], and as low as 0.3% in rural Guangdong province. Recently, however, the prevalence has risen rapidly, a trend first demonstrated by studies conducted in the Da Qing area of northeastern China. There, the prevalence in 1986 was 1.0%, but by 1994 it had increased over threefold to 3.5% [225, 226]. The 1994 survey of 200 000 people aged 25–64 years in 19 provinces that included Da Qing found overall prevalence rates of 2.3% for diabetes and 2.1% for impaired glucose tolerance. A community-based survey of 40 000 people aged 20–74 years in China between 1995 and 1997 confirmed this rising trend and also demonstrated urban–rural gradients in prevalence rates. Age-standardized prevalence rates were 3.2% for diabetes and 4.8% for impaired glucose tolerance, with the highest prevalence in provincial cities and the lowest in rural areas [227]. The International Collaborative Study of Cardiovascular Disease in Asia, conducted in 2000–2001, revealed a further increase in the prevalence of diabetes (undiagnosed and diagnosed) to 5.5%, with another 7.3% affected by impaired glucose tolerance [228] (Figure 5.4). Furthermore, among the 20 million Chinese people estimated to have diabetes based on fasting blood glucose, only 30% were previously diagnosed [228]. The large proportion of those with impaired glucose tolerance is particularly alarming. In the community-based Shanghai Diabetes Study, people with impaired glucose tolerance and/or impaired fasting glycaemia had an 11.7-fold increased risk of diabetes compared with those with normal glucose tolerance over a three-year follow-up period [229].

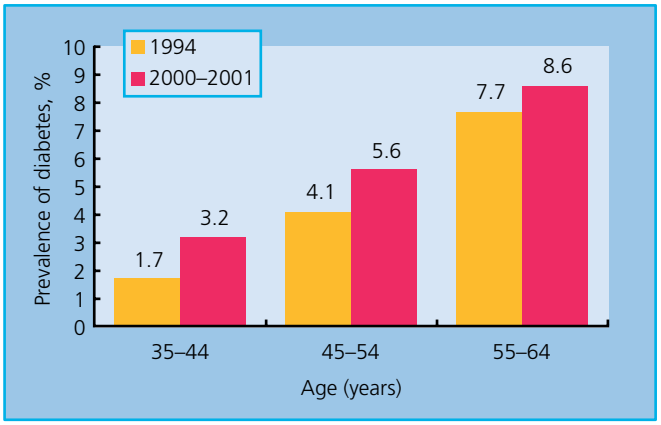

Figure 5.4 Changes in prevalence of diabetes among Chinese adults aged 35–64 years. Source: Data from the 1994 Chinese National Survey and the 2000–2001 InterASIA study; Gu et al. 2003 [228].

Chinese populations in affluent societies such as Hong Kong SAR, Singapore, Taiwan, and Mauritius all show higher prevalence rates compared with mainland China. In Hong Kong, the prevalence of diabetes increased from 8% to 10% between 1990 and 1995 [230, 231]. Studies in Taiwan indicate prevalence rates of 9–11%, although methodological discrepancies make direct comparisons difficult [224]. The annual incidence rate in Taiwan was reported in 1997 to be 1.8% [232]. In a review summarizing the findings from prevalence studies conducted in Chinese populations in 1995–2003, it was noted that Chinese people in Hong Kong and Taiwan have a 1.5–2.0-fold increased risk of diabetes adjusted for age and diagnostic criteria compared with their mainland counterparts [233].

The rapid increase in diabetes prevalence in China is likely to have been driven by the increase in obesity, particularly among children and adolescents [9, 234]. The 2002 National Nutrition and Health Survey noted a prevalence of overweight of 4.1% among children aged 7–12 years and 5.6% among those aged 12–18 years, with obesity rates of 2.5% and 1.6%, respectively [235]. In Hong Kong, a community-based study involving >2000 adolescents aged 11–18 years found alarming rates of obesity, with 8–10% of those aged 12–13 years fulfilling criteria for obesity [236]. In a national screening programme among schoolchildren in Taiwan between 1992 and 1999, the rate of newly identified diabetes was 9.0 per

100 000 for boys and 15.3 per 100 000 for girls. Obesity was found to be the major risk factor for the development of type 2 diabetes, where children with BMI in the ≥95th percentile had an ~19-fold increase in risk of type 2 diabetes compared with those with BMI in the <50th percentile [237].

Such alarming data for Chinese populations highlight the potential for further rises within China itself. Unless effective measures can be implemented, given the huge population of China, the consequences could be devastating. Indeed, two recent large nationwide epidemiological studies, involving >46 000 and 98 000 adults, respectively, reported diabetes prevalence rates of 9.7% in 2008 [238] and (if including elevated HbA_{1c} as a diagnostic criterion) 11.6% in 2010 [239]. This translates to a staggering estimate of 92.4 million individuals with diabetes and 148.2 million adults with pre-diabetes in China in 2008 [238].

South-East Asian Peninsula

There is considerable economic diversity within this region, although the recent emerging data showed that despite the relatively traditional lifestyle in many of the countries, diabetes is increasingly common within the region. A survey performed in two villages in Cambodia in 2004 revealed a diabetes prevalence rate of 5% in the rural community in Siem Reap but up to 11% in a semiurban community [240]. A study conducted in adults in Ho Chi Minh City in southern Vietnam indicated that the prevalence of diabetes increased substantially from 2.5% in 1993 to 3.8% in 2001 [241]. A more recent study using data from 2013 reported an age-standardized prevalence of 6.0% [242]. Similar increases have been reported in Indonesia [243] and the Philippines [244]. Prevalence rates in Thailand appear to be approaching those reported in Malaysia and Singapore, with prevalence of diabetes and impaired glucose tolerance in a 2004 national survey reported to be 6.7% and 12.5%, respectively [245].

In Singapore, serial studies since 1975 showed a rising prevalence of diabetes from 2% in 1975 to 4.7% in 1984, 8.6% in 1992, and 9% in 1998. Two more recent surveys indicate that the rate of rise may have stabilized. Ethnic Indians and Malays (especially Malay women) have the highest rates of diabetes (16.7–14.3%) and also the highest rates of obesity. A further 15% of the adult population have impaired glucose tolerance. In a survey conducted in 2004 by the Ministry of Health, Singapore, the prevalence of diabetes among the adult population was estimated to be 8.2% [246]. A more recent survey conducted by the Ministry of Health in 2010 noted a diabetes prevalence of 11.3% [247]. Obesity and adoption of a Westernized diet and lifestyle are again closely associated. Type 2 diabetes in childhood is also highlighted as an emerging problem. The prevalence of diabetes increased by more than twofold over 20 years in Malaysia, with the most recent nationwide survey reporting a prevalence of 22.6%, compared with a prevalence of 11.6% in 2006 [248].

Impact of diabetes

The epidemic of diabetes has a major impact on both personal and societal aspects. The major burden of diabetes stems from the treatment cost of its complications, such as stroke, blindness, coronary artery disease, renal failure, amputation, and infection. An estimated 6.7 million adults died of diabetes and its related diseases in 2021 [2]. Most people die from cardiovascular disease (particularly coronary artery disease and stroke) and end-stage renal disease. In a study on the trends in the incidence of diabetes-related complications in the USA, the rates of lower-extremity amputations, end-stage renal disease, acute myocardial infarction, stroke, and death from hyperglycaemic crisis declined from 1990 to 2010, although there remains a substantial healthcare burden due to the rising diabetes prevalence [94].

There are geographical differences in both the magnitude of these problems and their relative contributions to overall morbidity and mortality [242]. In white European and American populations, macrovascular complications, such as coronary artery disease and amputation, are major causes of disability. In contrast, end-stage renal disease and stroke are more prevalent among Chinese and Asian ethnic groups [13].

The occurrence of vascular complications of diabetes is related to the duration of hyperglycaemia. With the earlier onset of type 2 diabetes, more people will have an increased risk of developing these complications [249–251]. Despite the high prevalence of complications of diabetes and hence the high costs of management, simple, inexpensive measures are effective in preventing the development of diabetes and its vascular complications. Rather than merely focusing on the management of hyperglycaemia, global risk reduction with attention to cardiovascular risk factors has been found to be the most effective way of reducing the burden of diabetes. The challenge is to provide a platform whereby effective care can be delivered at an affordable cost [1].

Mortality and morbidity

Diabetes is associated with approximately twofold increased mortality in most populations, with the excess risk decreasing with increasing age [1, 252–254]. Although initial data suggest that the excess mortality associated with diabetes may be higher in Asian populations, this is probably related to differences in death certificate coding practices [255–257]. It was recently estimated that diabetes accounted for 12.2% of global all-cause mortality among people aged 20–79 years, with close to half of deaths due to diabetes being in people under the age of 60 years [2].

The most systematic comparative data, using standardized methodology, originate from the WHO Multinational Study of Vascular Disease in Diabetes, which has drawn from 14 centres in 13 countries since the 1980s. A follow-up report from 10 of these centres [258] shows that coronary heart disease and limb amputation rates varied 10–20-fold among different centres; there was also marked variation in the prevalence of clinical proteinuria and renal failure, but less variation in retinopathy and severe visual impairment. Striking features include the relative rarity of ischaemic heart disease and lower-extremity amputation in Hong Kong and Tokyo, contrasting with a high incidence of stroke, especially in Hong Kong. A high incidence of stroke was also found in Arizona and Oklahoma, the two Indigenous American centres. The highest rates of ischaemic heart disease were seen in the European centres, notably among women in Warsaw. Myocardial infarction was also common in Indigenous Americans, especially among men, while renal failure and proteinuria rates were highest among Indigenous Americans and in Hong Kong.

Other issues include the apparent vulnerability of Pacific Island populations to diabetes-related foot problems associated with neuropathy and of South Asians to coronary heart disease [42]. Importantly, the risk of coronary heart disease is already increased twofold at the stage of impaired glucose tolerance [259].

Another cause of morbidity and mortality that is increasingly recognized is the increased risk of cancer in people with diabetes. Various epidemiological studies in different populations have

suggested a link between diabetes and increased risk of pancreatic, hepatocellular, endometrial, breast, and colorectal carcinoma [260–262]. Although some of this may be due to the presence of common risk factors, such as obesity and dietary factors, a large prospective study demonstrated that cancer risk increases with increasing fasting glucose at baseline [263]. In a large population-based study in Australia, both type 1 diabetes and type 2 diabetes were associated with increased risk of incidence and mortality for cancer overall and for a number of site-specific cancers [264].

Intensive multifactorial interventions to reduce cardiovascular risk factors are effective in reducing cardiovascular mortality in diabetes [265, 266]. Although intensive blood glucose management does not lower cardiovascular mortality in the short term [267, 268], it may have beneficial effects in reducing cardiovascular and total mortality in the longer term, as suggested by long-term follow-up data from the UK Prospective Diabetes Study (UKPDS) [269]. It appears that the relative mortality of diabetes is decreasing in some countries [270, 271], and this may be related to the increased utilization of drugs to manage hyperlipidaemia, hyperglycaemia, and hypertension [272].

Healthcare burden and economic costs

The increase in the prevalence of diabetes, particularly among young adults, along with the increased morbidity and mortality associated with microvascular and macrovascular complications, is likely to lead to an escalation of healthcare costs and reduced economic growth. The IDF estimated that in 2021, diabetes-related health expenditure would reach US $379.5 billion in the USA, $165.3 billion in China, and $42.9 billion in Brazil [2]. The global health expenditure for diabetes in 2021 was estimated to be $966 billion, of which close to half would have been spent in North America (~$415 billion) and one-quarter in Asia ($241.3 billion). In the USA, the estimated total costs (direct and indirect) of diabetes increased from $23 billion in 1969 to $132 billion in 2002 [273, 274]. The cost of diabetes in the USA in 2007 was estimated by the ADA to be $174 billion, which includes $116 billion in excess medical expenditures and $58 billion in reduced national productivity [275]. These estimates were revised in 2017 to a total estimated cost of diagnosed diabetes of $327 billion, including $237 billion in direct medical costs and $90 billion in reduced productivity [97]. The largest components of medical expenditures attributed to diabetes are hospital inpatient care and medications to treat complications of diabetes and anti-diabetes medications, diabetes supplies, and more clinic visits [97]. However, the actual burden is likely to be even greater, since other non-monetary effects such as changes in quality of life, disability and suffering, care provided by unpaid caregivers, and other factors cannot be included in such analyses. The burden of diabetes affects all sectors of society, including higher insurance premiums paid by employees and employers, reduced earnings through productivity loss, and reduced overall quality of life for people with diabetes and their families and friends.

The cost of medical care for diabetes varies greatly among the different regions (Table 5.6). Although it is a very costly disease, interventions used to prevent or manage diabetes differ greatly in their cost-effectiveness [277]. The cost-effectiveness and feasibility of diabetes interventions in developing countries, as assessed by the World Bank, are listed in Table 5.7. Cost-effective interventions that are technically and culturally feasible should be implemented with the highest priority [278].

Table 5.6 Estimated direct medical costs of diabetes by region, 2003.

Region	Direct medical costs (US$ millions)	
	Low estimate	High estimate
Developing countries	12 304	23 127
East Asia and Pacific	1368	2656
Europe and Central Asia	2884	5336
Latin America and the Caribbean	4592	8676
Middle East and North Africa	2347	4340
South Asia	840	1589
Sub-Saharan Africa	273	530
Developed countries	116 365	217 760
World	128 669	240 887

Source: Adapted from Narayan et al. 2006 [276], Table 30.1.

Prevention of type 2 diabetes

There are entirely too many diabetic patients in the country. Statistics for the last thirty years show so great an increase in the number that, unless this were in part explained by a better recognition of the disease, the outlook for the future would be startling. Therefore, it is proper at the present time to devote attention not alone to treatment, but still more, as in the campaign against the typhoid fever, to prevention. The results may not be quite so striking or as immediate, but they are sure to come and to be important.

(Elliot Joslin, 1921)

Given the cost of diabetes, it is essential to prevent or delay the onset of diabetes and its associated complications. With improved understanding of the natural history of the development of type 2 diabetes and the role of various modifiable risk factors in its pathogenesis, several randomized clinical trials have examined the effect of lifestyle intervention to prevent type 2 diabetes. A large body of evidence has accumulated from these studies on the effectiveness of lifestyle measures in the prevention of diabetes, as summarized in Table 5.8. Most of these interventions include structured education and exercise programmes, reducing fat intake and increasing fibre intake, moderate exercise for at least 30 min per day, and moderate weight reduction of ≥5%. Importantly, in addition to being highly cost-effective, the effect of structured lifestyle intervention on reduction of diabetes risk appears to be maintained over a long duration of follow-up [269, 270]. In a follow-up of the China Da Qing Diabetes Prevention Study, participants who received lifestyle intervention had a 51% lower incidence of diabetes during the six-year active intervention period and a 43% lower incidence of diabetes over 20 years [285]. Furthermore, with follow-up extended to 23 years, those randomized to lifestyle intervention had a 41% reduction in cardiovascular mortality and a 29% reduction in all-cause mortality [280].

In addition to lifestyle intervention, several drugs used in the treatment of type 2 diabetes and obesity have been evaluated in clinical trials and are effective in preventing diabetes, including metformin, the thiazolidinedione class of compounds, acarbose, orlistat, and insulin itself (Table 5.9). The largest body of evidence for pharmacological prevention of diabetes is with metformin

Table 5.7 Summary of cost-effectiveness of interventions for treatment and prevention of diabetes.

Intervention	Cost/QALY (2001 US$)						Feasibility[a]	Implementing priority[b]
	East Asia and Pacific	Europe and Central Asia	Latin America and Caribbean	Middle East and North Africa	South Asia	Sub-Saharan Africa		
Level 1								
Glycaemic management in people with $HbA_{1c} \geq 9\%$ (75 mmol/mol)	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	++++	1
Blood pressure control in people with pressure >160/95 mmHg	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	++++	1
Footcare in people with a high risk of ulcers	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	++++	1
Level 2								
Pre-conception care for women of reproductive age	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	++	2
Lifestyle interventions for preventing type 2 diabetes	80	100	130	110	60	60	++	2
Influenza vaccinations among old people for type 2 diabetes	220	290	360	310	180	160	++++	2
Annual eye examination	420	560	700	590	350	320	++	2
Smoking cessation	870	1170	1450	1230	730	660	++	2
ACE inhibitor use for people with diabetes	620	830	1020	870	510	460	+++	2
Level 3								
Metformin intervention for preventing type 2 diabetes	2180	2930	3630	3080	1820	1640	++	3
Cholesterol management for people with total cholesterol >200 mg/dl (5.2 mmol/l)	4420	5940	7350	6240	3680	3330	+++	3
Intensive glycaemic management for people with $HbA_{1c} \geq 8\%$ (64 mmol/mol)	2410	3230	4000	3400	2000	1810	++	3
Screening for undiagnosed diabetes	5140	6910	8550	7260	4280	3870	++	3
Annual screening for microalbuminuria	3310	4450	5510	4680	2760	2500	++	3

[a] Feasibility was assessed based on difficulty of reaching the intervention population (the capacity of the healthcare system to deliver an intervention to the targeted population), technical complexity (the level of medical technologies or expertise needed for implementing an intervention), capital intensity (the amount of capital required for an intervention), and cultural acceptability (appropriateness of an intervention in terms of social norms and/or religious beliefs). ++++ indicates feasible for all four aspects, +++ indicates feasible for three of the four, ++ indicates feasible for two of the four, and + indicates feasible for one of the four.

[b] Implementing priority was assessed by combining the cost-effectiveness of an intervention and its implementation feasibility; 1 represents the highest priority and 3 represents the lowest priority.

ACE, angiotensin-converting enzyme; QALY, quality-adjusted life-year.

Source: Narayan et al. 2006 [276], Table 30.3.

Table 5.8 Summary of key randomized clinical trials using lifestyle intervention in the prevention of type 2 diabetes.

Study	No. of participants	Study participants	Duration (years)	Incidence in control (%)	RRR (%)	References
Da Qing (1997)	577	IGT	6	15.7	38	[279]
			Extended follow-up 23 yrs after randomization	89.9	45	[280]
DPS (2001)	522	IGT, BMI >25 kg/m^2	3.2	6	58	[127]
			Extended follow-up 7 yrs after start of study	7.4	43	[281]
DPP (2002)	3234	IGT, BMI >24 kg/m^2, FG >5.3 mmol/l	3	10	58	[282]
			Extended follow-up 10 yrs after randomization	5.3 per 100 person-years	34	[283]
Indian IDPP-1 (2006)	531	IGT	3	18.3	29	[166]
Japanese (2005)	458	IGT (men), BMI >24 kg/m^2	4	9.3	67	[284]

BMI, body mass index; DPP, Diabetes Prevention Programme; DPS, Diabetes Prevention Study (Finland); FG, fasting glucose; IDPP-1, Indian Diabetes Prevention Programme; IGT, impaired glucose tolerance; RRR, relative risk reduction.

Table 5.9 Randomized clinical trials assessing the effect of pharmacological interventions in the prevention of type 2 diabetes.

Drug	Trial	n	Follow-up (years)	Total dose	RR (95% CI)	References
Biguanides						
Metformin	DPP (2002)	2155	2.8	1700 mg/d	0.69 (0.57–0.83)	[282]
	CDPS (2001)	261	3	750 mg/d	0.23	[286]
	IDPP-1 (2006)	531	2.5	500 mg/d	0.74 (0.65–0.81)	[166]
Thiazolidinediones						
Troglitazone	TRIPOD (2002)	236	2.5	400 mg/d	0.45 (0.25–0.83)	[287]
	DPP	585	0.9	400 mg/d	0.25	
Rosiglitazone	DREAM (2006)	5269	3.0	8 mg/d	0.40 (0.35–0.46)	[288]
α-Glucosidase inhibitors						
Acarbose	STOP-NIDDM (2002)	1368	3.2	300 mg/d	0.75 (0.63–0.9)	[289]
Insulin						
Insulin glargine	ORIGIN	1456	6	Dose titrated up according to target, mean dose 0.4 units/kg/d	0.72 (0.58–0.91)	[290]

CDPS, Chinese Diabetes Prevention Study; CI, confidence interval; DPP, Diabetes Prevention Programme; DREAM, Diabetes Reduction Assessment with ramipril and rosiglitazone Medication; IDPP-1, Indian Diabetes Prevention Programme 1; *n*, number; ORIGIN, Outcome Reduction with Initial Glargine Intervention; RR, relative risk; STOP-NIDDM, Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus; TRIPOD, TROglitazone in the Prevention Of Diabetes.

treatment, which was associated with a ~40% reduction in risk of diabetes in a meta-analysis [291]. In addition, several clinical trials indicated that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers may reduce incident diabetes in high-risk people with hypertension [292–296]. A large randomized clinical trial compared the ACE inhibitor ramipril with placebo in people with impaired glucose tolerance or impaired fasting glycaemia. It did not show a significant reduction in incident diabetes after a median follow-up of three years, although ramipril was associated with increased regression to normoglycaemia [297]. In a recent pooled analysis of individual participant data from two phase 3, randomized, double-blind clinical trials, treatment with the sodium-glucose cotransporter 2 (SGLT-2) inhibitor dapagliflozin was associated with a 33% reduction in the development of type 2 diabetes over a median follow-up of 21.2 months [298].

Many pharmacological agents are currently in development or undergoing clinical trials for the treatment of type 2 diabetes or obesity, which should provide a constant supply of promising agents for evaluation in their effectiveness for preventing type 2 diabetes. At present, however, lifestyle intervention remains more cost-effective as a strategy for diabetes prevention. Recent prevention studies have also demonstrated the effectiveness of using mobile phone messaging or other aids to deliver support for lifestyle modification or person empowerment [299]. Among those who have morbid obesity, bariatric surgery has a significant impact on glycaemic levels and >60% of individuals with diabetes and severe obesity experience remission after gastric bypass surgery [300]. In the three-year follow-up of people with severe obesity who underwent bariatric surgery in the USA, the incidence of diabetes was 0.9% after Roux-en-Y gastric bypass and 3.2% after laparoscopic gastric banding [301].

Given the increased appreciation of the important role of the intrauterine environment and early development in modifying the risk of non-communicable diseases, it is increasingly recognized that pregnancy represents a critical period that requires optimal maternal nutrition [302], and also has long-term consequences for the health of the offspring. Therefore, diabetes and non-communicable disease prevention efforts now include

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considerations of primordial prevention, whereby measures to avoid the establishment of different environmental, social, behavioural, and physical exposures that may impair long-term health start early, including pre-conception and the pregnancy period [1, 303].

Remission of type 2 diabetes

While type 2 diabetes is traditionally considered to be an irreversible and progressive disease, the twin cycle hypothesis from Taylor in 2008 posited that type 2 diabetes arises as a result of long-term excessive energy intake, accompanied by accumulation of liver fat, hepatic insulin resistance, hyperinsulinemia, ectopic pancreatic fat accumulation, and impaired β-cell function [304]. It was therefore postulated that weight loss sufficient to reverse this may lead to durable remission of hyperglycaemia [305]. In a landmark proof of concept, 11 individuals with type 2 diabetes were started on a 600 kcal/d diet for eight weeks, during which they lost a mean 15 kg, and achieved normalization of hepatic insulin sensitivity, β-cell function, and blood glucose, accompanied by decreased liver and pancreas triacylglycerol stores [306]. In a subsequent open-label, cluster randomized trial in a primary care setting involving 306 participants with short duration of type 2 diabetes and BMI of 27–45 kg/m^2, of those who were recruited into a weight management programme involving caloric restriction and total diet replacement, withdrawal of diabetes and blood pressure medications, and structured support for long-term weight loss maintenance, 24% of participants in the intervention arm achieved a weight loss of ≥15 kg, while 46% of those in the intervention arm achieved diabetes remission [307]. A consensus report has now defined remission as HbA_{1c} <6.5% (48 mmol/mol) measured at least three months after cessation of glucose-lowering pharmacotherapy as the diagnostic criterion [308]. As there is an increasing number of programmes to implement caloric restriction and weight loss, as well as population-based studies on diabetes remission based on these criteria, future epidemiological studies would need to consider the impact of diabetes remission in consideration of diabetes prevalence.

More detailed discussion on epidemiological aspects of diabetes can be found elsewhere [309].

Conclusion

The interaction between genetic predisposition, the popularization of fast food, and a sedentary lifestyle, in addition to ageing of the general population, plays a major role in the increase in the prevalence of impaired glucose tolerance and type 2 diabetes globally. Countries in the Asia-Pacific and Africa regions with a growing economy will bear the major burden in the increase in number of people with diabetes. The significant increase in macro- and microvascular complications of diabetes places a heavy burden on healthcare resources. Studies have confirmed the benefit of intensive multifactorial risk management in reducing all-cause mortality and cardiovascular adverse events. Measures such as weight reduction and exercise are effective in preventing the progression of impaired glucose tolerance to diabetes. Hence, despite being one of the commonest chronic diseases, diabetes can be prevented or managed effectively with interventions that are relatively cost-effective compared with the cost of treating the micro- and macrovascular complications.

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2 Normal Physiology

6 Overview of Glucose Metabolism

Richard I.G. Holt

Professor in Diabetes & Endocrinology, Human Development and Health, University of Southampton, Faculty of Medicine, Southampton, UK

Honorary Consultant Physician, Southampton National Institute for Health Research Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK

Key points

- Under normal physiological conditions, blood glucose levels are maintained within narrow limits.
- The tight regulation of glucose is necessary because some tissues, particularly the brain, are highly dependent on glucose as an energy source.
- Insulin, produced by the β cells of the pancreatic islet, is the key hormone involved in the regulation of cellular energy supply and macronutrient balance derived from food. Insulin increases the uptake and storage of glucose in liver, adipose tissue, and skeletal muscle.
- Several hormones including glucagon, catecholamines, corticosteroids, and growth hormone antagonize the actions of insulin and are collectively known as the counter-regulatory hormones.
- The key insulin-sensitive tissues are the liver, skeletal muscle, and adipose tissue.
- The liver is the principal organ of glucose homeostasis; in the post-absorptive state, the liver stores glucose as glycogen, a large highly branched glucose polymer. The liver also possesses the ability to produce glucose for utilization by other tissues by breaking down glycogen (glycogenolysis) or *de novo* glucose synthesis (gluconeogenesis).
- Muscle glycogen synthesis accounts for ~90% of insulin-stimulated whole-body glucose disposal and for virtually all the non-oxidative glucose disposal in healthy humans.
- The incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), act as β-cell sensitizers potentiating glucose-induced insulin secretion when glucose concentrations are above 4–5 mmol/l and suppressing glucagon secretion in a similarly glucose-dependent manner.
- The gastrointestinal system influences glucose metabolism through the microbiome, a diverse collection of over 1000 bacterial species that live within the gut, through as yet poorly defined mechanisms.
- The brain plays an important role in coordinating the multiple responses from pancreas, liver, and other tissues to regulate glucose levels.
- The kidney makes a unique contribution to glucose homeostasis by controlling glucose reabsorption from renal tubules following glomerular filtration and, apart from the liver, is the only organ with sufficient gluconeogenic enzyme activity to contribute to gluconeogenesis.

Under normal physiological conditions, blood glucose levels are maintained within narrow limits and in health rarely stray outside the range of 3.5–8.0 mmol/l (63–144 mg/dl). This is despite wide variations in glucose supply during eating and demand during fasting and exercise. The tight regulation of glucose is necessary because some tissues, particularly the brain, are highly dependent on glucose as an energy source. The brain relies on glucose as its primary fuel source and utilizes ~20% of whole-body glucose supplies, despite constituting only ~2% of total body weight (Chapter 10) [1]. Its requirement is 1 mg/kg body weight per minute, or ~100 g daily in a 70 kg person. The brain requires a continuous supply of glucose from the circulation for normal function because it can neither synthesize glucose nor store more than a few minutes' supply as glycogen. Furthermore, it is unable to use alternative fuel sources such as amino acids, ketones, and lactate effectively at physiological concentrations. Glucose uptake by the brain is not dependent on insulin, but is obligatory depending on an adequate glucose concentration to cross into the brain.

By contrast, the body cannot tolerate high glucose concentrations, because these irreversibly damage cellular proteins and cause irreversible tissue damage, as is seen in people with diabetes-related microvascular complications (Chapter 42). The body has developed a highly complex feedback system involving multiple organs including the brain, pancreatic islets, liver, and other tissues that coordinate the regulation of glucose homeostasis (Figure 6.1).

The following chapters in this section describe how individual tissues and hormones regulate glucose. Rather than repeat what follows, this chapter is short by design, but its purpose is to provide an overview of glucose metabolism.

Pancreatic islets of langerhans

Mammalian pancreatic islets typically contain ~1000 endocrine cells; these cells include the β cells (~60% of adult human islet cells) that produce insulin, α cells (20–30%) that produce glucagon,

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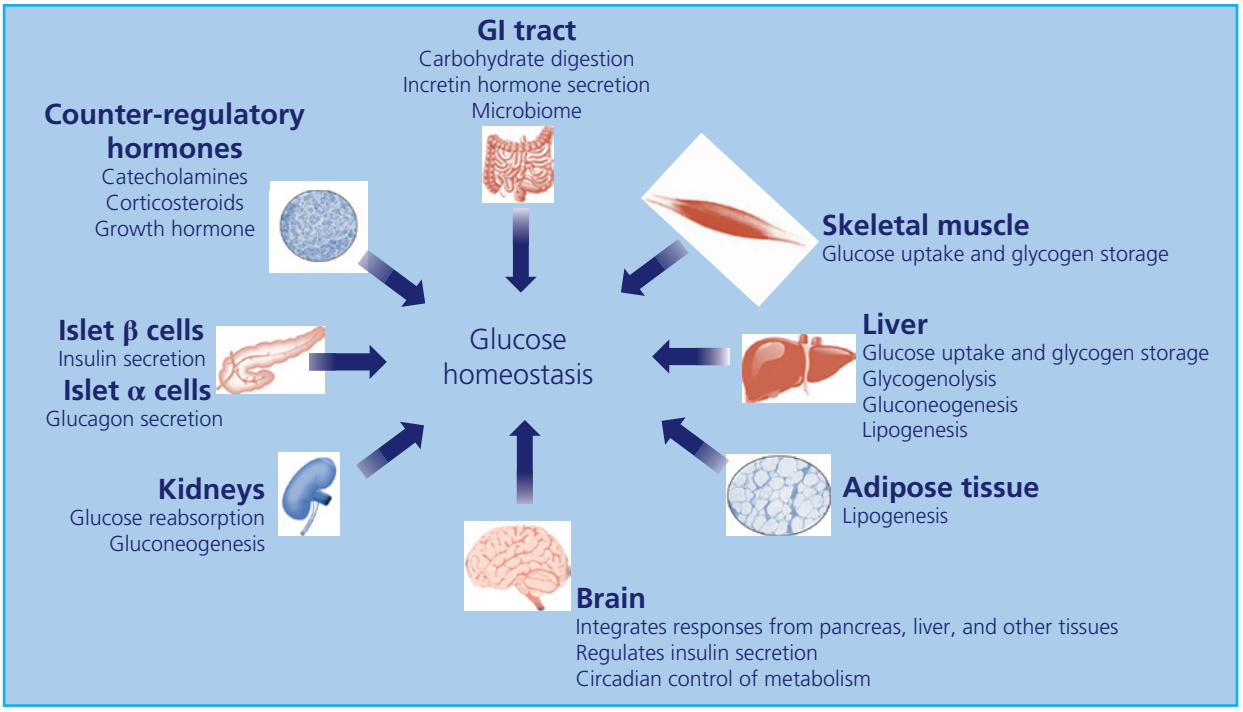

Figure 6.1 Tissues involved in glucose homeostasis. GI, gastrointestinal.

somatostatin-expressing δ cells (~10%), and cells expressing pancreatic polypeptide (<5%), ghrelin, and peptide YY (<1%) (see Figure 7.1). Islets are highly vascularized, receiving up to 15% of the pancreatic blood supply despite accounting for only 2–3% of the total pancreatic mass and are well supplied by autonomic nerve fibres [2].

Insulin

Insulin is the key hormone involved in the regulation of cellular energy supply and macronutrient balance derived from food and may be considered as the hormone that signals the *post-meal* fed state. Insulin secretion is influenced by many factors (Table 6.1), but food ingestion is the most important. After a meal, once glucose concentrations rise above 5 mmol/l, insulin is secreted in a coordinated pulsatile fashion into the portal vein in a characteristic biphasic pattern; first there is an acute rapid *first-phase* release of insulin, lasting for a few minutes, followed by a less intense but more sustained *second phase* (Chapter 7). Insulin is also produced during the fasting state; although at a low level, this background secretion accounts for ~50% of total daily insulin production.

Insulin exerts its biological actions by binding to the insulin receptor, which is a heterotetrameric transmembrane protein comprising two α- and two β-glycoprotein subunits linked by disulfide bonds (Chapter 9). Following binding to the α subunits, insulin induces a conformational change in the β subunits, resulting in activation of tyrosine kinase and initiation of a cascade response involving a host of other intracellular substrates. The insulin-receptor complex is then internalized by the cell, insulin is degraded, and the receptor is recycled to the cell surface.

Effect on glucose metabolism

Insulin is involved in the regulation of carbohydrate metabolism at many steps (Table 6.2), but predominantly acts to increase the uptake and storage of glucose in liver, adipose tissue, and skeletal

Table 6.1 Factors regulating insulin release from the β cells of the pancreatic islets.

Factor	Insulin secretion increased by	Insulin secretion decreased by
Nutrients	Raised glucose Amino acids Fatty acids	Low glucose
Islet products	Glucagon Adenine nucleotides Divalent cations	Somatostatin Ghrelin PYY
Neurotransmitters	Acetylcholine through parasympathetic stimulation Norepinephrine via sympathetic α-receptors VIP PACAP GRP	Norepinephrine via sympathetic β receptors Dopamine NPY Galanin
Gastrointestinal hormones	Cholecystokinin GIP GLP-1	Somatostatin Ghrelin
Adipokines	Adiponectin	Leptin Resistin
Stress		Exercise Hypoxia Hypothermia Surgery Severe burns

GIP, glucose-dependent insulinotropic peptide (previously known as gastric inhibitory peptide); GLP-1, glucagon-like peptide 1; GRP, gastrin-releasing polypeptide; NPY, neuropeptide Y; PACAP, pituitary adenylate cyclase activating polypeptide; PYY, peptide tyrosine tyrosine; VIP, vasoactive intestinal polypeptide.

Table 6.2 Insulin actions on carbohydrate metabolism.

Action	Mechanism
Increases glucose uptake into cells	Translocation of glucose transporter (GLUT) 4 to the cell surface
Increases glycogen synthesis	Activates glycogen synthase by dephosphorylation
Inhibits glycogen breakdown	Inactivates glycogen phosphorylase and its activating kinase by dephosphorylation
Inhibits gluconeogenesis	Dephosphorylation of pyruvate kinase and 2,6-biphosphate kinase
Increases glycolysis	Dephosphorylation of pyruvate kinase and 2,6-biphosphate kinase
Converts pyruvate to acetyl co-enzyme A	Activates the intramitochondrial enzyme complex pyruvate dehydrogenase

muscle. Cell membranes are not inherently permeable to glucose and require a family of specialized glucose-transporter (GLUT) proteins to carry glucose through the membrane into cells [3]. The function of GLUT1 to 3 is insulin independent, but insulin stimulates glucose uptake into muscle and adipose tissue through GLUT4. GLUT4 is normally present in the cytoplasm, but after insulin binds to its receptor, GLUT4 moves to the cell surface where it creates a pore for glucose entry.

Effect on lipid metabolism

Insulin promotes fat storage within adipose tissue and the liver by increasing the rate of lipogenesis and controlling the formation and storage of triglyceride [4]. The critical step in lipogenesis is the activation of the insulin-sensitive lipoprotein lipase in the capillaries. This enzyme acts to release fatty acids from circulating chylomicrons or very low-density lipoproteins, which are taken up into the adipose tissue. Lipogenesis is also facilitated by glucose uptake, because its metabolism by the pentose phosphate pathway provides nicotinamide adenine dinucleotide phosphate (NADPH), which is needed for fatty acid synthesis.

Insulin increases triglyceride synthesis by activating acetyl co-enzyme A (CoA) carboxylase, while at the same time suppressing fat oxidation through the inhibition of carnitine acyltransferase (Table 6.3). Insulin also stimulates triglyceride synthesis through the esterification of glycerol phosphate. By contrast, triglyceride breakdown is suppressed by insulin by inhibiting hormone-sensitive lipase. Within the liver, insulin reduces ketogenesis (Chapter 41). Cholesterol synthesis is increased by insulin through activation and dephosphorylation of hydroxymethylglutaryl co-enzyme A (HMGCoA) reductase, while cholesterol ester breakdown appears to be inhibited by dephosphorylation of cholesterol esterase.

Table 6.3 Insulin actions on fatty acid metabolism.

Action	Mechanism
Releases fatty acids from circulating chylomicrons or very low-density lipoproteins	Activates lipoprotein lipase
Increases fatty acid synthesis	Activates acetyl CoA carboxylase
Suppresses fatty acid oxidation	Inhibits carnitine acyltransferase
Increases triglyceride synthesis	Stimulates esterification of glycerol phosphate
Inhibits triglyceride breakdown	Dephosphorylates hormone-sensitive lipase
Increases cholesterol synthesis	Activates and dephosphorylates HMGCoA reductase
Inhibits cholesterol ester breakdown	Dephosphorylates cholesterol esterase

CoA, co-enzyme A; HMGCoA, hydroxymethylglutaryl co-enzyme A.

Effect on protein metabolism

Insulin stimulates amino acid uptake into cells and promotes protein synthesis in a range of tissues by increasing transcription of specific mRNA and translation into proteins on the ribosomes [5]. Examples of enhanced mRNA transcription include glucokinase and fatty acid synthase. By contrast, insulin decreases mRNA-encoding liver enzymes such as carbamoyl phosphate synthetase, which is a key enzyme in the urea cycle. However, the major action of insulin on protein metabolism is to inhibit protein breakdown. In this way, it acts synergistically with growth hormone and insulin-like growth factor I (IGF-I) to increase protein anabolism.

Glucagon

Glucagon is made predominantly in islet α cells and regulates glycaemia through actions in the liver and islet β cell (Chapter 8). Its secretion is stimulated by a fall in blood glucose and by amino acids. Release of glucagon is also under neural control; sympathetic adrenergic activation increases glucagon release while the parasympathetic nervous system inhibits its release. Local control within the islet and signals from the gastrointestinal tract are also important; insulin and somatostatin inhibit glucagon release while glucagon stimulates its own release in an autocrine matter. The gastrointestinal incretin hormones, glucose-dependent insulinotropic peptide (GIP) stimulates and glucagon-like peptide-1 (GLP-1) inhibit glucagon secretion.

Glucagon has direct actions on hepatocytes to promote glucose production, and lipid and amino acid metabolism. It plays an important role in preventing significant hypoglycaemia during fasting, stress, and exercise by antagonizing the actions of insulin. Following binding to specific glucagon receptors in the liver, glucagon mobilizes glycogen and enhances glucose production from non-carbohydrate precursors by gluconeogenesis. At the same time, glucagon promotes lipid oxidation within the liver. Glucagon has central effects where it inhibits food intake and increases resting energy expenditure.

Liver

The liver is the principal organ of glucose homeostasis and receives absorbed monosaccharides directly from the intestine via the portal vein [6]. In the post-absorptive state, the liver stores glucose as glycogen, a large highly branched glucose polymer. Initially glucose enters the hepatocyte and is phosphorylated to glucose 6-phosphate, which may subsequently follow a number of metabolic pathways, including glycogen synthesis, the hexosamine pathway, the pentose phosphate pathway, and oxidative routes (Figure 6.2). Approximately 50% of ingested glucose is stored as glycogen during the post-prandial period in healthy people. The capacity to store glycogen is limited and so excess dietary glucose is converted into fat by hepatic *de novo* lipogenesis [7].

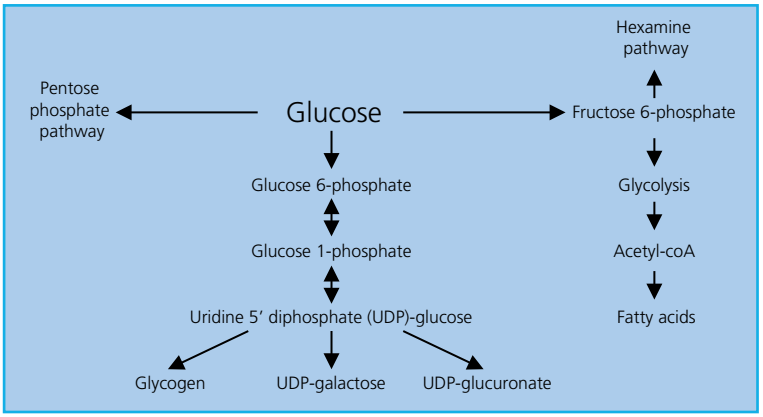

Figure 6.2 Glucose metabolic pathways. coA, co-enzyme A.

The liver possesses the ability to produce and release glucose into the systemic circulation for utilization by other tissues, particularly during periods of fasting. The formation of glycogen is a reversible process and glycogen can be easily metabolized to glucose when needed through a process known as glycogenolysis. Although glucose is mainly derived from the diet, the body can also synthesis glucose *de novo* from non-carbohydrate sources, through a process known as gluconeogenesis. The liver is responsible for the production of more than 90% of the glucose derived from gluconeogenesis. The principal gluconeogenic precursors are pyruvate and lactate, certain gluconeogenic amino acids, and glycerol from fat metabolism. During short-term periods of fasting, glycogenolysis is the predominant component of hepatic glucose output. However, during prolonged periods of fasting, the glycogen reserve and glycogenolysis gradually diminish while gluconeogenesis becomes increasingly important.

Skeletal muscle and adipose tissue

Tissues such as muscle and fat have insulin-responsive glucose transporters and absorb glucose in response to post-prandial peaks in glucose and insulin. Glucose taken up by muscle is stored as glycogen or metabolized to lactate or carbon dioxide and water. Muscle glycogen synthesis accounts for ~90% of insulin-stimulated whole-body glucose disposal and for virtually all the non-oxidative glucose disposal in healthy insulin-sensitive humans [8]. Glycogen storage is a reversible process and glycogen can be easily metabolized to glucose when needed (glycogenolysis). Glucose is metabolized through glycolysis and the Krebs cycle to produce adenosine triphosphate (ATP) to supply the cell with energy. Insulin stimulates glycolysis and enhances the irreversible conversion of pyruvate to acetyl CoA, which may then be directly oxidized via the tricarboxylic acid (Krebs') cycle, or used for fatty acid synthesis. Although the contribution of adipose cells to glucose disposal is smaller than that of skeletal muscle, adipose tissue is a highly dynamic organ that nevertheless plays an important role in glucose and lipid homeostasis.

Gastrointestinal tract

Glucose is derived mainly from foods in the diet containing carbohydrates or sugars. The process of digestion begins in the mouth by both mechanical processes, such as chewing, and chemical breakdown by the action of specific enzymes, such as α-amylase and α-glucosidase. Sugars within food may be polysaccharides, such as starch or glucagon, disaccharides (sucrose, lactose, and maltose), or monosaccharides (glucose, fructose, and galactose) (Figure 6.3). The end products of digestion are monosaccharides, which are absorbed across the membrane of the small intestine into the circulation and transported for storage or use as energy.

Several factors affect the rate of carbohydrate digestion and absorption, such as the food composition and other foods eaten at the same time [9]. The glycaemic index (GI) is a scale that ranks carbohydrate-rich foods as *high GI*, *medium GI*, and *low GI* based on the rate at which glucose-containing carbohydrates are digested and absorbed and consequently increase blood glucose concentrations [10]. High GI foods are digested and absorbed more quickly and lead to a larger increase in post-prandial blood glucose level than low GI foods. Other food factors affecting the rate of carbohydrate absorption are shown in Table 6.4.

Incretin hormones

Nearly 100 years ago, injected extracts of the small intestinal mucosa were shown to exert a hypoglycaemic effect, leading to speculation that the gastrointestinal tract produced hormones that could regulate glucose homeostasis (Chapter 36). Further evidence for this

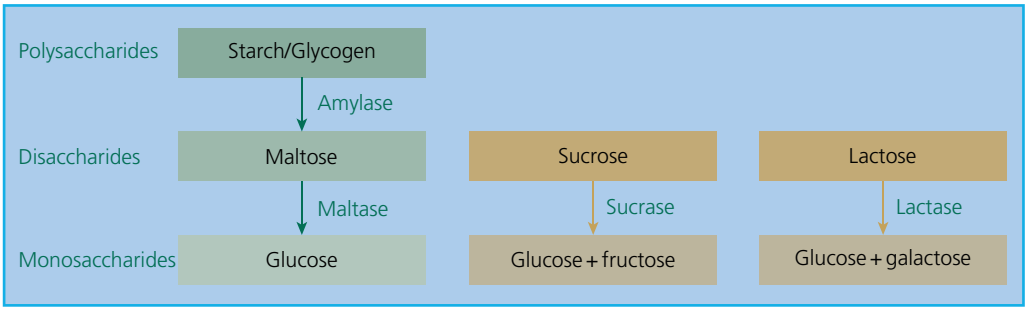

Figure 6.3 Carbohydrate digestion.

A L G r a w a n y

Table 6.4 Food factors affect the rate of carbohydrate absorption.

Factors that increase the rate of absorption	Factors that reduce the rate of absorption
Cooking	Food processing
Simultaneous consumption of fat and protein	
High fibre content	
Food containing acid	

hypothesis came from the observation that orally administered glucose evoked a greater insulin response than intravenously administered glucose, the so-called *incretin effect* [11]. Although other hormones may contribute, two incretin hormones, GIP and GLP-1, are mainly responsible for this effect.

GLP-1 is produced following meal ingestion by the enteroendocrine L cells. Within 5–15 minutes of eating, plasma GLP-1 concentrations start to rise, and peak after 45–60 minutes. GLP-1 is rapidly degraded within minutes by the enzyme dipeptidyl peptidase-4, which is widely expressed and is highly active in the liver, the intestinal and renal brush border membranes, and the lungs. The main way in which GLP-1 contributes to glucose homeostasis is through its actions on pancreatic islet cell function. GLP-1 acts as a β-cell sensitizer, potentiating glucose-induced insulin secretion when glucose concentrations are above 4–5 mmol/l [12]. GLP-1 also suppresses glucagon secretion in a similarly glucose-dependent manner [13]. Beyond its actions on the β cell, GLP-1 slows gastric emptying, to limit delivery of nutrients to the small intestines from the stomach, reducing postprandial plasma glucose excursions [14]. GLP-1 has a further indirect effect on glucose metabolism by its action in the hypothalamus to signal satiety and reduce appetite and food intake [15].

GIP is synthesized by K cells of the duodenum and jejunum [16]. Like GLP-1, it is stimulated by food ingestion, is broken down by DPP-4 and stimulates insulin secretion in a glucose-dependent manner. In contrast to GLP-1, however, it stimulates glucagon secretion. GIP also regulates appetite and satiety.

Microbiome

A further way in which the gastrointestinal system influences glucose metabolism is through the microbiome, which comprises a diverse collection of over 1000 bacterial species that live within the gut (Chapter 19). The microbiome differs between individuals and its composition may be influenced by numerous factors, including diet, medication, and hygiene. The precise mechanisms by which the microbiome influences glucose homeostasis are yet to be elucidated, but the microbiome has the potential to activate immune pathways, which interact with insulin signalling pathways and glucose homeostasis as well as regulating enteroendocrine cell function, incretin signalling, and the composition of the bile acid pool and downstream signalling pathways [17].

Brain

Given the brain's reliance on glucose for fuel, it is unsurprising that the brain has evolved mechanisms that ensure a continuous supply of glucose (Chapter 10). The brain plays an important role in coordinating the multiple responses from pancreas, liver, and other tissues that occur following the ingestion of a meal, limiting plasma glucose excursion in the post-prandial state. The brain, which is capable of sensing changes in glucose, modifies insulin secretion through alterations of autonomic tone to pancreatic islets [18]. Connections between the brain and islet cells involve both the sympathetic nervous system and parasympathetic nervous system [19] (see Figure 10.2) and can rapidly influence both insulin and glucagon secretion in response to changes in the level of circulating nutrients and other stimuli under physiological conditions [20]. The *cephalic phase* of insulin release, whereby insulin is secreted in anticipation of a meal, provides an example of how the brain controls insulin secretion. In addition to the direct effects on the pancreas, the brain also activates insulin-independent mechanisms that lower blood glucose levels, including both suppression of endogenous glucose production and increased hepatic glucose uptake [21].

Glucose metabolism is affected by the circadian rhythm under the influence of the brain. A system of *clock* genes within the suprachiasmatic nucleus is entrained to the light–dark cycle that aligns many behaviours and metabolic functions to the circadian clock. One example is hepatic insulin sensitivity, which decreases during sleep but increases upon waking and the expectation of breakfast [22].

Kidney

The kidney performs an important and distinctive role in glucose homeostasis, through both glucose utilization and production [23]. Apart from the liver, the kidney is the only organ with sufficient gluconeogenic enzyme activity to contribute significant amounts of glucose to the circulation via gluconeogenesis. The kidney may be responsible for up to 20% of all glucose production and 40% of gluconeogenesis, although 10% is more usual. Renal gluconeogenesis adapts to various nutritional and hormonal stimuli. Compared with the liver, renal gluconeogenesis is more sensitive to insulin and catecholamines, whereas glucagon has little to no effect. In contrast to the liver, the kidney increases glucose release after glucose ingestion.

The kidney also makes a unique contribution to glucose homeostasis by controlling glucose reabsorption from renal tubules following glomerular filtration (Chapter 35). Plasma glucose is neither protein bound nor complexed with macromolecules and is therefore freely filtered by the glomerulus, with up to 180 g/d filtered under normal physiological conditions [24]. This would lead to an excessive and unsustainable urinary loss of glucose if not recovered, and so an important adaptive response conserves glucose in normal situations by reabsorbing almost all of the filtered glucose in the proximal tubule through an insulin-independent process. The amount of glucose reabsorbed is dependent on the amount filtered, but the maximal reabsorptive capacity, the renal threshold for glucose, is reached once the circulating glucose concentration is ~11 mmol/l. The renal threshold varies between individuals and is affected by renal function, age, pregnancy, insulin resistance, and glycaemic levels, among others.

Glucose is reabsorbed in the proximal tubules by the sodium–glucose co-transporter 2 (SGLT2), with ~10% being reabsorbed by SGLT1 (Figure 6.4) [25]. The SGLTs belong to a broader group of solute carriers called SLC5, which currently has six SGLT members [26]. SGLT1 and SGLT2 are the best characterized and are differentiated from other SGLTs by their high capacity to transport glucose. SGLT1 has a relatively higher affinity for glucose [27], but

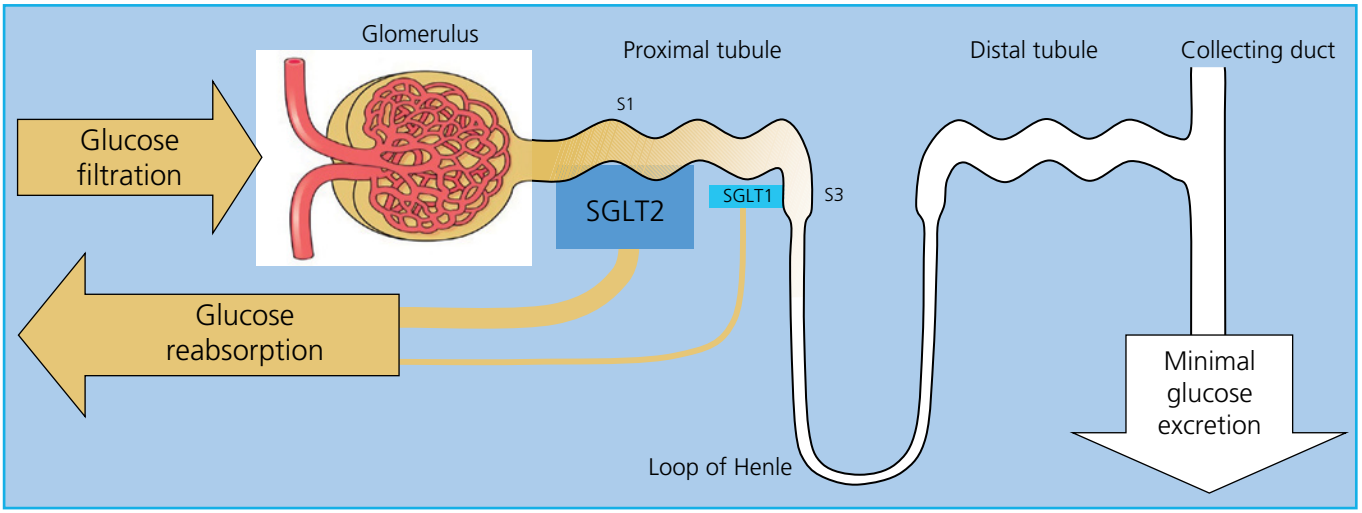

Figure 6.4 Normal physiology of renal glucose filtration and reabsorption. SGLT, sodium–glucose co-transporter.

transports less glucose than SGLT2 because it is only expressed in the third segment of the proximal tubule, whereas SGLT2 is abundantly expressed in the first two segments as well [26]. SGLT-2 transfers one sodium ion with one glucose molecule down an electrochemical gradient for sodium, generated by, for example, the activity of an Na^+–K^+ ATPase pump [28]. SGLTs are expressed in other tissues in the body: SGLT1 is the main intestinal glucose transporter and is also found in the heart and trachea, whereas SGLT2 is primarily found in renal tissues but has also been isolated in the ileum, brain, and liver [24].

Other hormones involved in glucose metabolism

In addition to glucagon, several hormones including growth hormone, cortisol, and catecholamines antagonize the effects of insulin. These hormones are released in response to falling glucose concentrations as part of the *counter-regulatory response to defend the body against hypoglycaemia* [1]. As plasma glucose declines, there is a decrease in insulin secretion followed by release of glucagon and adrenaline and then cortisol and growth hormone. The combined action of the counter-regulatory response is to increase glucose concentrations by stimulating gluconeogenesis and glycogenolysis while reducing peripheral glucose utilization. The symptoms associated with the release of these hormones prompt a behavioural response to ingest food.

Catecholamines

Adrenaline influences glucose homeostasis through two main mechanisms to inhibit insulin secretion and increase hepatic glucose output (Chapter 22). In pancreatic β cells, adrenaline acts via stimulation of α_2 adrenoceptors [29]. In the liver, the actions of adrenaline are mediated by β_2 adrenoceptors. There is a transient increase in glycogenolysis and a more sustained effect on gluconeogenesis [30–32]. As well as a direct effect on the liver, adrenaline also drives hepatic gluconeogenesis by increasing adipose tissue lipolysis, providing the precursors lactate, alanine, and glycerol needed for gluconeogenesis. Adipose tissue lipolysis is stimulated via the β_1- and β_3-adrenoceptors. Impaired glucose utilization in muscle is mediated through direct β_2-adrenergic effects, which may explain why adrenaline is more potent in producing hyperglycaemia than noradrenaline, because the former has a higher affinity for β_2-receptors [30–32].

Corticosteroids

The effect of glucocorticoids on glucose metabolism results from multiple pathways including β-cell function and insulin resistance [33]. Acutely glucocorticoids impair β-cell function, although this can recover somewhat with prolonged exposure [34]. Glucocorticoids directly impair insulin-mediated glucose uptake by interfering with components of the insulin signalling cascade, including glycogen synthase kinase-3, glycogen synthase, and GLUT4 translocation [35]. Furthermore, glucocorticoids increase glucose level indirectly through their actions on fat metabolism. Phosphoenolpyruvate carboxykinase (PEPCK) is a key enzyme that regulates fatty acid release from adipose tissue and synthesis of triacylglycerol from fatty acids and glycerol 3-phosphate [36]. Glucocorticoids inhibit PEPCK in adipose, but increase its action in the liver; this leads to an increase in circulating free fatty acids in the blood, which in turn interferes with glucose utilization and results in insulin resistance, especially in skeletal muscle.

Growth hormones and insulin-like growth factor I

The effect of growth hormone on glucose metabolism is complicated by its interplay with insulin-like growth factor (IGF-I) [37]. Growth hormone increases fasting hepatic glucose output, by increasing hepatic gluconeogenesis and glycogenolysis, and decreases peripheral glucose utilization through the inhibition of glycogen synthesis and glucose oxidation [38]. Furthermore, growth hormone stimulates lipolysis with the release of glycerol and free fatty acids. However, growth hormone also increases the production of IGF-I, which has insulin-like actions that are, in the case of glucose metabolism, opposite to those of growth hormone. The precise role of growth hormone and IGF-I and their interactions with insulin in regulating normal glucose homeostasis remain unknown, but glucose metabolism is frequently deranged in situations where growth hormone is either deficient or in excess. The IGF-binding proteins (IGFBPs) have a further modifying role on glucose homeostasis, particularly IGFBP-1, which is inversely related to insulin concentration and has a diurnal variation, with the highest concentrations being overnight when insulin levels are lowest [39].

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7 Islet Function and Insulin Secretion

Peter M. Jones and Shanta J. Persaud
Department of Diabetes, King's College London, London, UK

Key points

- Regulation of fuel homeostasis in mammals is dependent on numerous small endocrine organs known as islets of Langerhans, which are located in the pancreas.
- Islets contain β cells, which are the only source of the polypeptide hormone insulin.
- Islet β cells are equipped to detect changes in circulating nutrients.
- Elevated levels of nutrients initiate an insulin secretory response from β cells that results in the storage of circulating nutrients in liver, muscle, and adipose tissue.
- A wide range of other signals, including hormones, neurotransmitters, and neuropeptides, can modify the insulin secretory response to circulating nutrients.
- Complex interactions between islet cells, the autonomic nervous system, and gastrointestinal incretin hormones allow precise integration between metabolic fuel intake, usage, and storage.

The German anatomy student Paul Langerhans first described in 1869 the 'islands of clear cells' distributed throughout the pancreas [1], but he did not realize the physiological significance of these cell clusters, which are today known as islets of Langerhans. We now know that islets are the endocrine compartment of the pancreas, comprising ~2–3% of the total pancreatic volume. Islets are approximately spherical (Figure 7.1a), with an average diameter of 100–200 μm, and a healthy human pancreas may contain up to a million individual islets, each having its own complex anatomy, blood supply, and innervation.

Islet structure and function

Islet anatomy

A typical mammalian islet comprises ~1000 endocrine cells including the insulin-expressing β cells (~60% of adult human islet cells), glucagon-expressing α cells (20–30%), somatostatin-expressing δ cells (~10%), and cells expressing pancreatic polypeptide (<5%), ghrelin, and peptide YY (<1%). The anatomical arrangement of islet cells varies between species. In rodents, the majority β-cell population forms a central core surrounded by a mantle of α and δ cells (Figure 7.1a), but human islets show less well-defined organization, with α and δ cells also being located throughout the islet (Figure 7.1b) [2,3]. Advances in high-throughput functional and molecular phenotyping have demonstrated that human islets show considerable molecular, anatomical, and functional heterogeneity, which may be important in the islet dysfunction associated with the development of type 2 diabetes [4].

Islets are highly vascularized and receive up to 15% of the pancreatic blood supply, despite accounting for only 2–3% of the total pancreatic mass. Each islet is served by an arteriolar blood supply that penetrates the mantle to form a capillary bed in the islet core. Earlier studies using vascular casts of rodent islets suggested that the major route of blood flow through an islet was from the inner β cells to the outer α and δ cells [5], but later studies using optical imaging of fluorescent markers to follow islet blood flow *in vivo* [6] revealed more complex patterns of both inner-to-outer and top-to-bottom blood flow through the rodent islet. Imaging studies in human islets suggest that most β cells are in direct contact with capillaries and are structurally polarized to target insulin secretion towards the capillary bed [3].

Islets are well supplied by autonomic nerve fibres and terminals containing the classic neurotransmitters acetylcholine and norepinephrine, along with a variety of biologically active neuropeptides [7, 8]. Vasoactive intestinal polypeptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) are localized with acetylcholine to parasympathetic nerves, where they may be involved in mediating prandial insulin secretion and the α-cell response to hypoglycaemia [9]. Other neuropeptides, such as galanin and neuropeptide Y (NPY), are found with norepinephrine in sympathetic nerves, where they may have a role in the sympathetic inhibition of insulin secretion, although there are marked interspecies differences in the expression of these neuropeptides [7].

Intra-islet interactions

The anatomical organization of the islet has a profound influence on the ability of the β cells to recognize and respond to physiological signals [10–12], and numerous studies have demonstrated important

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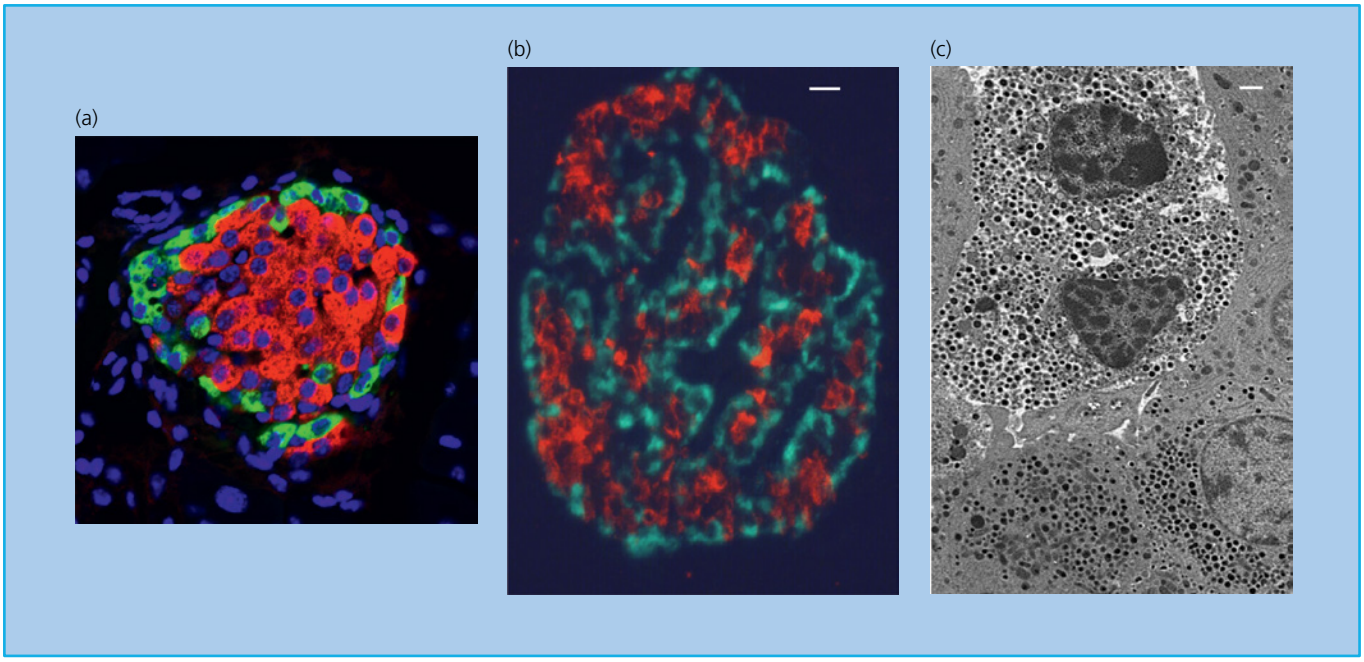

Figure 7.1 Anatomy of the islet of Langerhans. (a) Mouse islet. The image shows a section through a mouse pancreas in which insulin and glucagon are identified by red and green immunofluorescence, respectively, demonstrating the typical β-cell core surrounded by a thin mantle of α cells. In mouse islets, β cells comprise ~80% of the endocrine cell mass. Scale bar is 10 μm. (b) Human islet. The image shows a section through a human pancreas in which insulin and glucagon are identified by red and green immunofluorescence, respectively, demonstrating the less organized structure of the human islet when compared with mouse islets. In human islets, β cells comprise ~50–60% of the endocrine cell mass. Scale bar is 10 μm. (c) Transmission electron micrograph of human islet cells. The image shows a transmission electron micrograph of several cells within a human islet. The two cells at the top with the electron-dense secretory granules surrounded by a clear halo are β cells. The cells in the lower part of the micrograph are α cells. Scale bar is 2 μm. Source: Authors' unpublished data.

roles for islet α cells and δ cells in the regulation of human β-cell function. Islet cells have the potential to communicate through several mechanisms, although their relative importance is still uncertain [13]. Islet cells are functionally coupled through a network of gap junctions, and gene deletion studies in mice have highlighted the importance of gap-junctional coupling via connexin 36 in the regulation of insulin secretory responses [14, 15]. Cell-to-cell contact through cell-surface adhesion molecules in localized microdomains offers an alternative communication mechanism [16], and interactions mediated by E-cadherin [16–18] or ephrins [19] have been implicated in the regulation of β-cell function. Components of the intra-islet extracellular matrix, which is predominantly synthesized by islet endothelial cells and pericytes [20], influence β-cell gene expression [20], proliferation, survival, and function via interactions with integrins on the β-cell surface [21]. A further important level of control is exerted via numerous intra-islet paracrine and autocrine effects in which a biologically active substance released by one islet cell can influence the functional status of a neighbouring cell (paracrine), or of itself (autocrine) [22]. Figure 7.2 shows some of the molecules that have been implicated in this type of intra-islet cell–cell communication. Thus, islet cells can interact with each other via the classic islet hormones: insulin, glucagon, and somatostatin [23–28]; via other products secreted by the endocrine cells, including neurotransmitters [29], peptides such as kisspeptin [30], glucagon-like peptide 1 (GLP-1) [29, 31], and urocortin3 (Ucn3) [32], and adenine nucleotides and divalent cations that are co-released with insulin [33–36]; and via other less well-known mechanisms, including the generation of gaseous signals such as nitric oxide and carbon monoxide [37–39]. This plethora of potential intra-islet interactions may reflect the requirement for coordinating the secretory responses of many individual islet cells to generate the rate and pattern of hormone secretion appropriate to the prevailing physiological conditions. However, much of the experimental evidence is derived from isolated islets *in vitro*, which, lacking a microcirculation, may not be an appropriate model for the *in vivo* situation [40].

Insulin biosynthesis and storage

The ability to release insulin rapidly in response to metabolic demand, coupled with the relatively slow process of producing polypeptide hormones, means that β cells are highly specialized for the production and storage of insulin, to the extent that insulin comprises ~10% (~10 pg/cell) of the total β-cell protein.

Biosynthesis of insulin

In humans, the gene encoding pre-proinsulin, the precursor of insulin, is located on the short arm of chromosome 11 [41]. It is 1355 base pairs in length and its coding region comprises three exons: the first encodes the signal peptide at the N-terminus of pre-proinsulin, the second the B-chain and part of the C-(connecting)-peptide, and the third the rest of the C-peptide and the A-chain (Figure 7.3). Transcription and splicing to remove the sequences encoded by the introns yield a messenger RNA of 600 nucleotides, translation of which gives rise to pre-proinsulin, an 11.5-kDa polypeptide. The cellular processes and approximate timescales involved in insulin biosynthesis, processing, and storage are summarized in Figure 7.4.

Pre-proinsulin is rapidly (<1 minute) discharged into the cisternal space of the rough endoplasmic reticulum, where proteolytic enzymes immediately cleave the signal peptide, generating

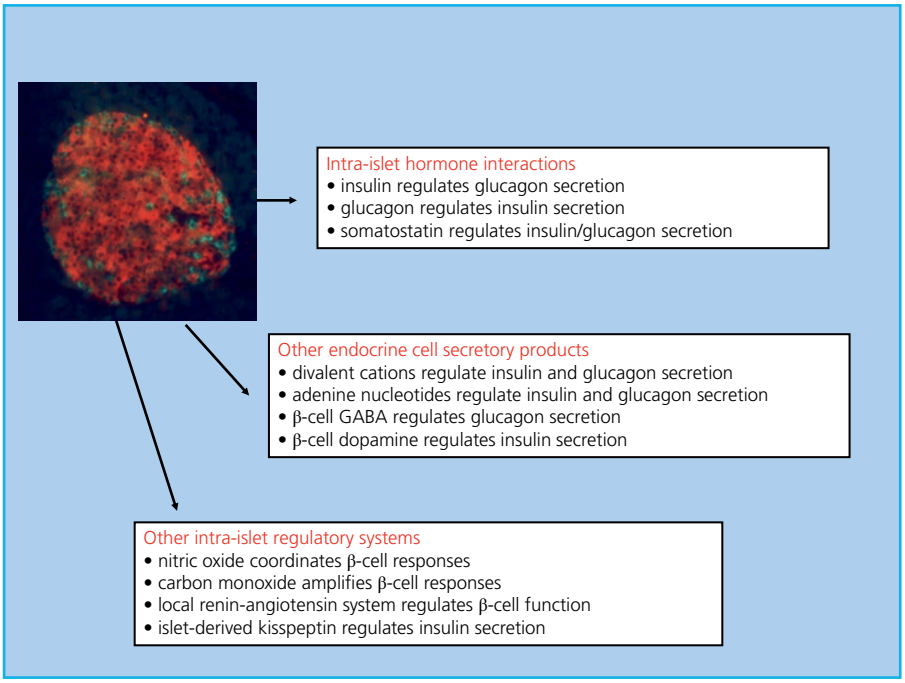

Figure 7.2 Intra-islet autocrine–paracrine interactions. The heterogeneous nature and complex anatomy of the islet permit numerous interactions between islet cells that are mediated by the release of biologically active molecules.

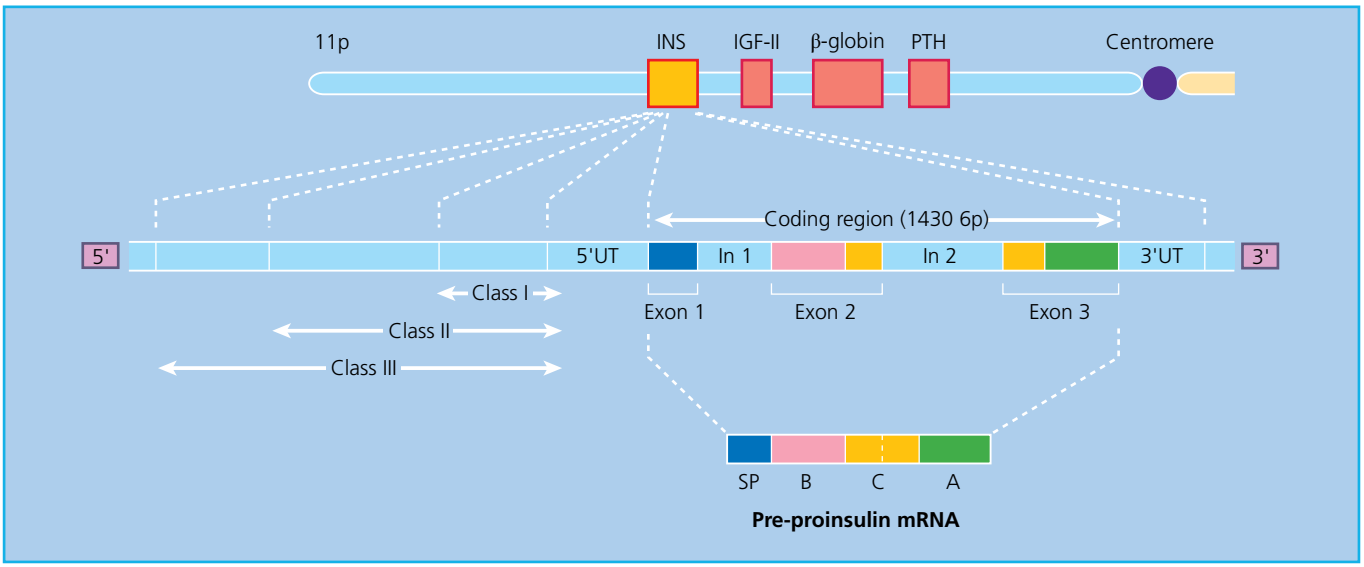

Figure 7.3 Structure of the human insulin gene. The coding region of the human insulin (INS) gene comprises three exons, which encode the signal peptide (SP), B-chain, C-peptide, and A-chain. The exons are separated by two introns (In1 and In2). Beyond the 5′ untranslated region (5′UT), upstream of the coding sequence, lies a hypervariable region in which three alleles (classes I, II, and III) can be distinguished by their size. IGF-II, insulin-like growth factor II; PTH, parathyroid hormone.

proinsulin. Proinsulin is a 9-kDa peptide, containing the A- and B-chains of insulin (21 and 30 amino acid residues, respectively) joined by the C-peptide (30–35 amino acids). The structural conformations of proinsulin and insulin are very similar, and a major function of the C-peptide is to align the disulfide bridges that link the A- and B-chains so that the molecule is correctly folded for cleavage (Figure 7.5). Proinsulin is transported in microvesicles to the Golgi apparatus, where it is packaged into membrane-bound vesicles known as secretory granules. The conversion of proinsulin to insulin is initiated in the Golgi complex and continues within the maturing secretory granule through the sequential action of two endopeptidases (prohormone convertases 2 and 3) and carboxypeptidase H [42], which remove the C-peptide chain, liberating two cleavage dipeptides and finally yielding insulin (Figure 7.5). Insulin and C-peptide are stored together in the secretory granules and are ultimately released in equimolar amounts by a process of regulated exocytosis. Under normal conditions, >95% of the secreted product is insulin (and C-peptide) and <5% is released as proinsulin.

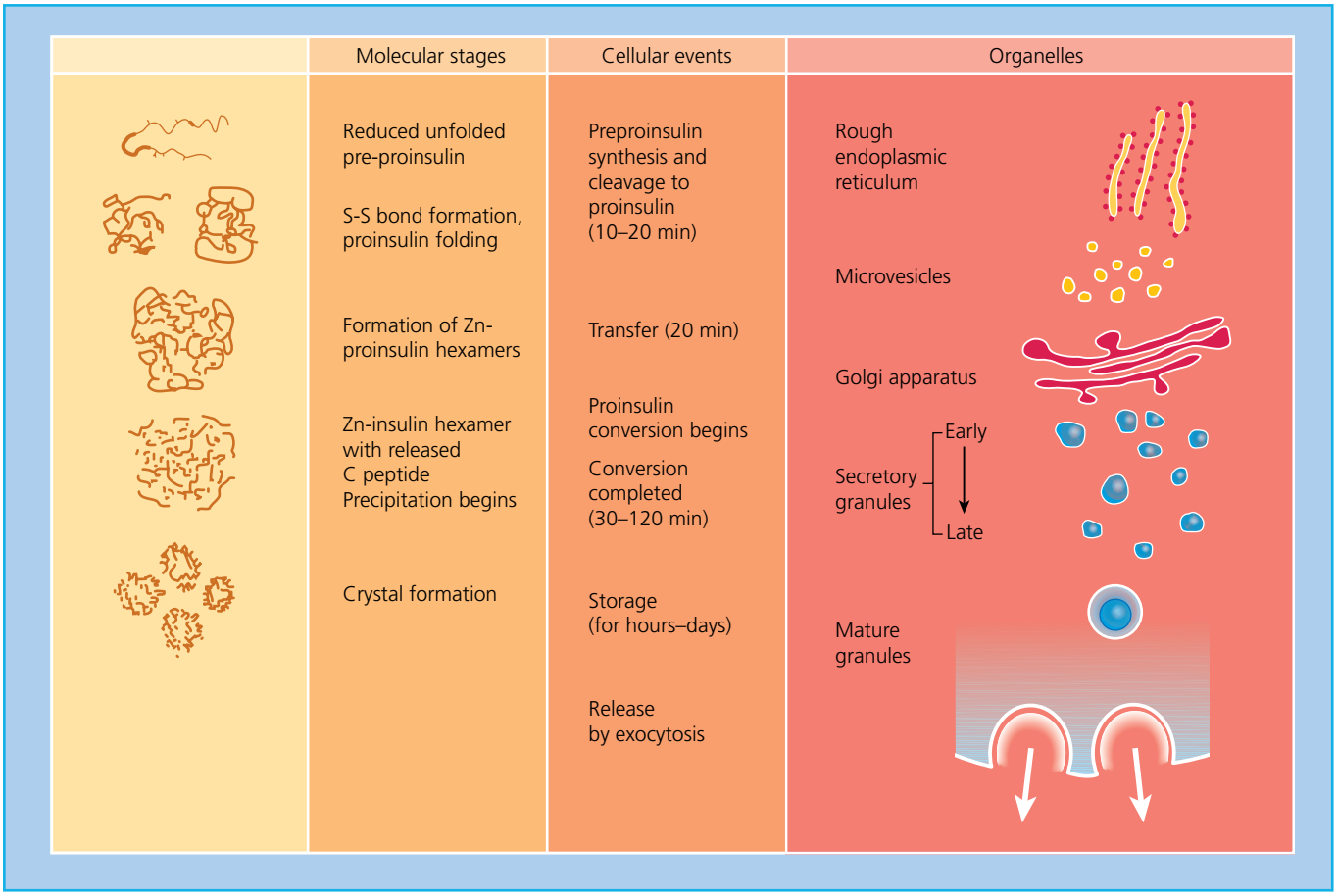

Figure 7.4 The intracellular pathways of proinsulin biosynthesis, processing, and storage. The molecular folding of the proinsulin molecule, its conversion to insulin, and the subsequent arrangement of the insulin hexamers into a regular pattern are shown on the left. The time course of the various processes and the organelles involved are also shown.

However, the secretion of incompletely processed insulin precursors (proinsulin and its *split* products; Figure 7.5) is increased in some individuals with type 2 diabetes.

The β cell responds to increases in the circulating concentrations of nutrients by increasing insulin production in addition to increasing insulin secretion, thus maintaining insulin stores [42]. Acute (<2 hours) increases in the extracellular concentration of glucose and other nutrients result in a rapid and dramatic increase in the transcription of pre-proinsulin mRNA and in the rate of proinsulin synthesis [43]. There is a sigmoidal relationship between glucose concentrations and biosynthetic activity, with a threshold glucose level of 2–4 mmol/l. This is slightly lower than the threshold for the stimulation of insulin secretion (~5 mmol/l), which ensures an adequate reserve of insulin within β cells.

Storage and release of insulin

The insulin secretory granule has a typical appearance in electron micrographs, with a wide space between the crystalline electron-opaque core and its limiting membrane (Figure 7.1c). The major protein constituents of the granules are insulin and C-peptide, which account for ~80% of granule protein [44], with numerous minor components including peptidases, peptide hormones, and a variety of (potentially) biologically active peptides of uncertain function [44, 45]. Insulin secretory granules also contain high concentrations of divalent cations, such as zinc (~20 mmol/l), which is important in the crystallization and stabilization of insulin within the granule [46]. Zinc is transported into the insulin secretory granules by the islet-specific zinc transporter ZnT8, where it binds to insulin to form a crystalline lattice of insoluble hexamers. Polymorphisms in the *SLC30A8* gene encoding ZnT8, in which a single nucleotide polymorphism (SNP) generates a ZnT8 variant with lower Zn^{2+} transporting activity, are associated with increased risk of type 2 diabetes [47]. However, deletion of *SLC30A8* in a number of transgenic mouse models produces only modest effects on insulin storage and secretion, and on whole-body glucose homeostasis, so the mechanistic link between *SLC30A8* polymorphisms and type 2 diabetes risk remains unclear [47]. The intragranular functions of calcium (~120 mmol/l) and magnesium (~70 mmol/l) are uncertain, but they are co-released with insulin on exocytosis of the secretory granule contents, so they may have extracellular signalling roles via the cell-surface calcium-sensing receptor [33]. Similarly, the adenine nucleotides found in insulin secretory granules (~10 mmol/l) may have a signalling role when they are released into the extracellular space [34].

The generation of physiologically appropriate insulin secretory responses requires complex mechanisms for moving secretory granules from their storage sites within the cell to the specialized sites for exocytosis on the inner surface of the plasma membrane, and the role of cytoskeletal elements, notably microtubules and microfilaments, in the intracellular translocation of insulin storage

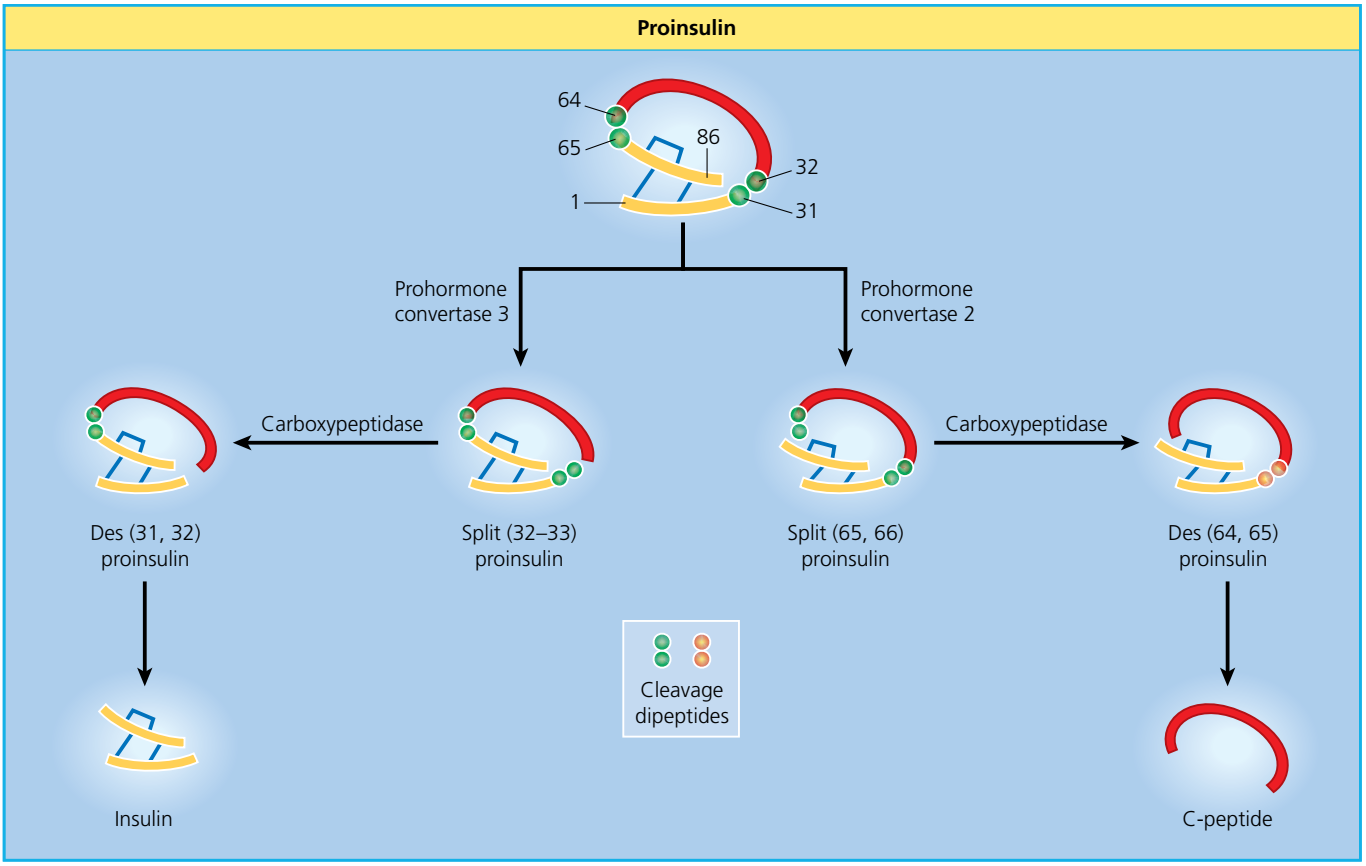

Figure 7.5 Insulin biosynthesis and processing. Proinsulin is cleaved on the C-terminal side of two dipeptides, namely Arg^{31}-Arg^{32} (by prohormone convertase 3) and Lys^{64}-Arg^{65} (prohormone convertase 2). The cleavage dipeptides are liberated, so yielding the 'split' proinsulin products and ultimately insulin and C-peptide.

granules has been studied extensively [48, 49]. Microtubules are formed by the polymerization of tubulin subunits and normally form a network radiating outwards from the perinuclear region [50]. The microtubular network is in a process of continual remodelling and the dynamic turnover of tubulin, rather than the total number of microtubules, is an important regulator of insulin secretion. Recent studies have implicated the microtubule-associated protein tau as a key player in the glucose-induced remodelling of β-cell microtubules, and hence insulin secretion [51].

The microtubule framework may provide the pathway for the secretory granules, but microtubules do not provide the motive force so other contractile proteins are likely to be involved. Actin is the constituent protein of microfilaments and exists in cells as a globular form of 43 kDa and as a filamentous form (F-actin), which associates to form microfilaments. F-actin remodelling in β cells is regulated by agents that alter rates of insulin secretion, and the pharmacological disruption of microfilament formation inhibits insulin secretion [52]. Myosin light and heavy chains are expressed at high concentrations in β cells, suggesting that actin and myosin may interact to propel granules along the microtubular network, and a myosin- and Rab-interacting protein (MyRIP) has been implicated in cyclic adenosine monophosphate (cAMP)–dependent insulin secretion through interaction with the motor protein MyoVa [53]. It is likely that other molecular motors, including myosin 5a, kinesins, and dynein [51, 54–56], are also involved in the movement of secretory granules, and perhaps other organelles, in β cells.

Insulin is released from secretory granules by exocytosis, a process in which the granule membrane and plasma membrane fuse together, releasing the granule contents into the interstitial space. Much of our knowledge of the molecular mechanisms of exocytosis is derived from studies of neurotransmitter release from nerve cells, and similar mechanisms operate in β cells, although some proteins implicated in synaptic vesicle exocytosis are not required for release of β-cell secretory granules [57]. The docking of the granules at the inner surface of the plasma membrane is via the formation of a multimeric complex of proteins known as the SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor) complex, which comprises proteins associated with secretory granules and the plasma membrane, and soluble fusion proteins [52, 58, 59]. The docked granules will fuse with the membrane and release their contents only in the presence of elevated intracellular calcium levels, which are sensed by synaptotagmins, a class of calcium-binding granule proteins [58, 60]. Secretory granules are distributed throughout the β-cell cytoplasm (Figure 7.1c), and it is likely that the transport of granules from distant sites to the plasma membrane is regulated independently from the final secretory process, with a reservoir of pre-docked granules available at the inner surface of the plasma membrane. Fusion of this readily releasable pool of granules may account for the rapid first-phase release of insulin in response to glucose stimulation, and direct electrophysiological measurements have demonstrated that the β-cell exocytotic response comprises a short-lived first phase with a very rapid rate of granule exocytosis from the

readily releasable pool, followed by a sustained second phase with a slower rate of exocytosis, from a reserve pool [61]. A key role for the regulatory protein Munc18c in the β-cell secretory granule fusion complex was identified in experiments where its knockdown in human β cells led to significant reductions in exocytosis of granules of both the readily releasable and reserve pools [62].

Regulation of insulin secretion

To ensure that circulating levels of insulin are appropriate for the prevailing metabolic status, β cells are equipped with mechanisms to detect changes in circulating nutrients and hormone levels, and in the activity of the autonomic nervous system [63]. Moreover, β cells have fail-safe mechanisms for coordinating this afferent information and responding with an appropriate secretion of insulin. The major physiological determinant of insulin secretion in humans is the circulating concentration of glucose and other nutrients, including amino acids and fatty acids. These nutrients possess the ability to initiate an insulin secretory response: when nutrients are absorbed from the gastrointestinal system, the β cell detects the changes in circulating nutrients and releases insulin to enable their uptake and metabolism or storage by the target tissues. The consequent decrease in circulating nutrients is detected by the β cells, which switch off insulin secretion to prevent hypoglycaemia. The β-cell responses to nutrient initiators of insulin secretion can be modified by various hormones and neurotransmitters, which act to amplify, or occasionally inhibit, the nutrient-induced responses (Table 7.1). Under normoglycaemic conditions, these agents have little or no effect on insulin secretion, a mechanism that prevents inappropriate secretion of insulin, which would result in potentially harmful hypoglycaemia. These agents are often referred to as potentiators of insulin secretion to distinguish them from nutrients that initiate the secretory response. The overall insulin output depends on the relative input from initiators and potentiators at the level of individual β cells, on the synchronization of secretory activity between β cells in individual islets, and on the coordination of secretion between the hundreds of thousands of islets in a human pancreas. This section considers the mechanisms employed by β cells to recognize and respond to nutrient initiators and non-nutrient potentiators of insulin secretion.

Table 7.1 Key non-nutrient regulators of insulin secretion.

Stimulators	Inhibitors
Islet products	
Glucagon/GLP-1	SST-14
Adenine nucleotides	Ghrelin
Divalent cations	PYY
Neurotransmitters	
Acetylcholine	Norepinephrine
VIP	Dopamine
PACAP	NPY
GRP	Galanin
Gastrointestinal hormones	
CCK	SST-28
GIP	Ghrelin
GLP-1	
Adipokines	
Adiponectin	Leptin
	Resistin

CCK, cholecystokinin; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide-1; GRP, gastrin-releasing polypeptide; NPY, neuropeptide Y; PACAP, pituitary adenylate cyclase-activating polypeptide; PYY, peptide tyrosine tyrosine; SST, somatostatin; VIP, vasoactive intestinal polypeptide.

Nutrient-induced insulin secretion

Nutrient metabolism

Islet β cells respond to small changes in extracellular glucose concentrations within a narrow physiological range and the mechanisms through which β cells couple changes in nutrient metabolism to regulated exocytosis of insulin are becoming increasingly well understood. Glucose is transported into β cells via high-capacity glucose transporters (GLUT; GLUT2 in rodents, GLUT1, 2, and 3 in humans [64, 65]), enabling rapid equilibration of extracellular and intracellular glucose concentrations. Once inside the β cell, glucose is phosphorylated by glucokinase, which acts as the *glucose sensor*, coupling insulin secretion to the prevailing glucose level [66], although evidence is accumulating of other metabolic amplifiers of insulin secretion, notably the anaplerotic flux of pyruvate to oxaloacetate and beyond [63]. The dose–response curve of glucose-induced insulin secretion from isolated islets is sigmoidal (Figure 7.6) and is determined primarily by the activity of glucokinase. Glucose concentrations below 5 mmol/l do not affect rates of insulin release, and the rate of secretion increases progressively at extracellular glucose levels between 5 and ~15 mmol/l, with half-maximal stimulation at ~8 mmol/l. The time course of the insulin secretory response to elevated glucose is characterized by a rapidly rising but transient first phase, followed by a maintained and prolonged second phase, as shown in Figure 7.7. This profile of insulin secretion is obtained whether insulin levels are measured following a glucose load *in vivo*, or whether the secretory output from the perfused pancreas or isolated islets is assessed, suggesting that the characteristic biphasic secretion pattern is an intrinsic property of the islets.

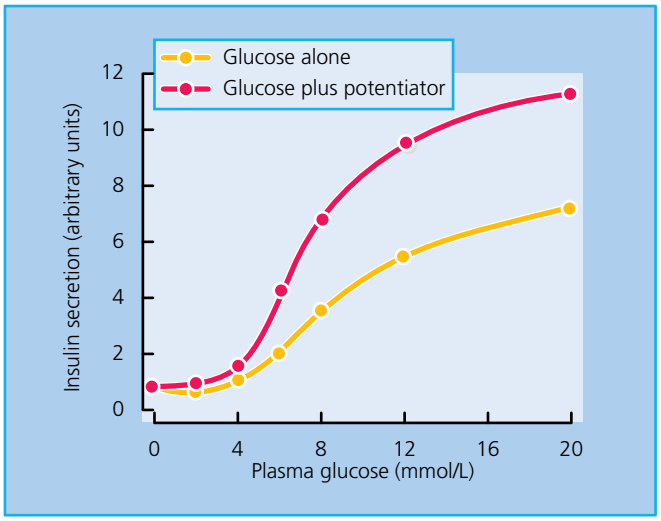

Figure 7.6 Glucose-induced insulin secretion from islets of Langerhans. No stimulation is seen below a threshold value of ~5 mmol/l glucose. Potentiators amplify insulin secretion at stimulatory concentrations of glucose, but are ineffective at subthreshold glucose levels.

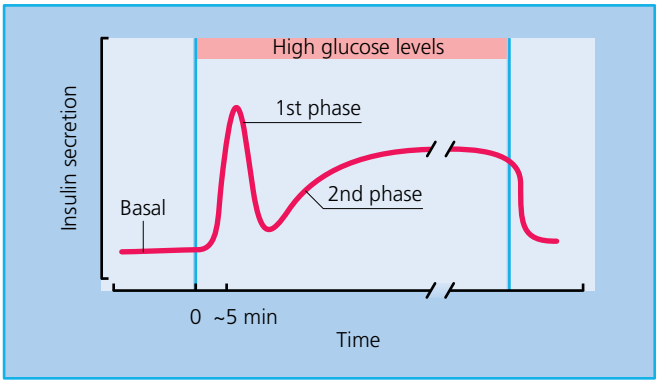

Figure 7.7 Glucose-induced insulin release *in vitro*. The image shows the pattern of glucose-induced insulin secretion from perfused pancreas, in response to an increase in the glucose concentration. An acute first phase, lasting a few minutes, is followed by a sustained second phase of secretion that persists for the duration of the high-glucose stimulus. A similar biphasic pattern of glucose-induced insulin secretion is seen in isolated rodent and human islets, suggesting that this characteristic pattern of insulin secretion is an intrinsic property of the islets.

ATP-sensitive potassium channels and membrane depolarization

In the absence of extracellular glucose, the β-cell membrane potential is maintained close to the potassium equilibrium potential by the efflux of potassium ions through inwardly rectifying potassium channels. These channels were called ATP-sensitive potassium (K_{ATP}) channels, because application of adenosine triphosphate (ATP) to the cytosolic surface of β-cell membrane patches resulted in rapid, reversible inhibition of resting membrane permeability to potassium ions [67]. This property of the K_{ATP} channel is pivotal in linking glucose metabolism to insulin secretion. Thus, ATP generation following glucose metabolism, in conjunction with concomitant lowering of adenosine diphosphate (ADP) levels, leads to closure of β-cell K_{ATP} channels. Channel closure and the subsequent reduction in potassium efflux promote depolarization of the β-cell membrane and influx of calcium ions through voltage-dependent L-type calcium channels. The resultant increase in cytosolic Ca^{2+} triggers the exocytosis of insulin secretory granules, thus initiating the insulin secretory response (Figure 7.8).

At around the time that the K_{ATP} channels were established as the link between the metabolic and electrophysiological effects of

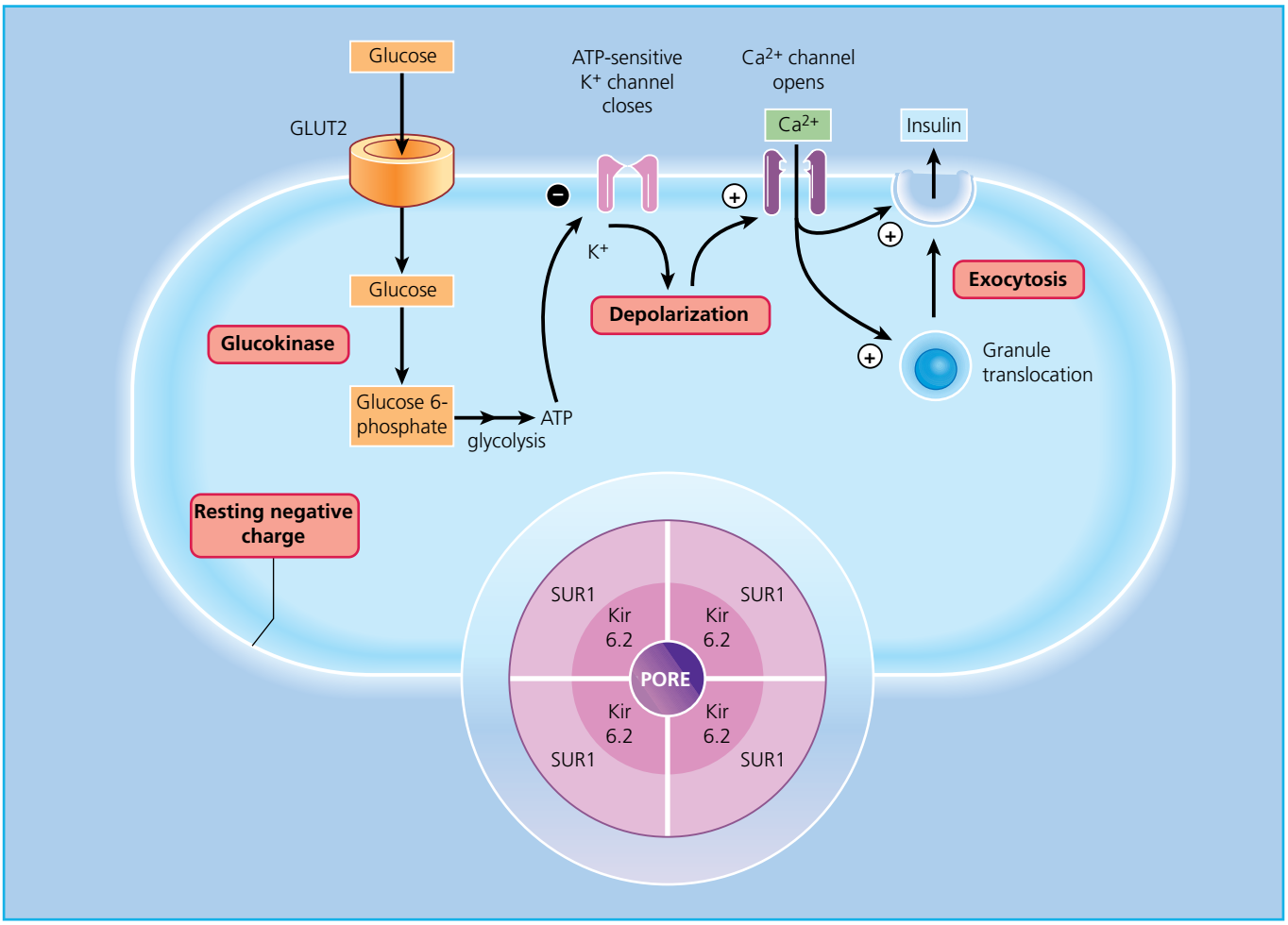

Figure 7.8 Intracellular mechanisms through which glucose stimulates insulin secretion. Glucose is metabolized within the β cell to generate adenosine triphosphate (ATP), which closes ATP-sensitive potassium channels in the cell membrane. This prevents potassium ions from leaving the cell, causing membrane depolarization, which in turn opens voltage-gated calcium channels in the membrane and allows calcium ions to enter the cell. The increase in cytosolic calcium initiates granule exocytosis. Sulfonylureas act downstream of glucose metabolism, by binding to the SUR1 component of the K_{ATP} channel (inset). GLUT, glucose transporter.

glucose, they were also identified as the cellular target for sulfonylureas. The capacity of sulfonylureas to close K_{ATP} channels explains their effectiveness in type 2 diabetes where the β cells no longer respond adequately to glucose, as the usual pathway for coupling glucose metabolism to insulin secretion is bypassed. The β-cell K_{ATP} channel is a hetero-octamer formed from four potassium channel subunits (termed Kir6.2) and four sulfonylurea receptor subunits (SUR1) [68]. The Kir6.2 subunits form the pore through which potassium ions flow and these are surrounded by the SUR1 subunits, which have a regulatory role (Figure 7.8). ATP and sulfonylureas induce channel closure by binding to Kir6.2 and SUR1 subunits, respectively, while ADP activates the channels by binding to a nucleotide-binding domain on the SUR1 subunit. Diazoxide, an inhibitor of insulin secretion, also binds to the SUR1 subunit to open the channels. The central role of K_{ATP} channels in β-cell glucose recognition makes them obvious candidates for β-cell dysfunction in type 2 diabetes. Early studies in people with type 2 diabetes, maturity-onset diabetes of the young (MODY), or gestational diabetes failed to detect any *Kir6.2* gene mutations that compromised channel function [69, 70]. Since then, larger-scale studies of variants in genes encoding *Kir6.2* and *SUR1* have demonstrated polymorphisms associated with increased risk of type 2 diabetes [71]. Similarly, activating mutations in the *Kir6.2* gene are causal for cases of permanent neonatal diabetes (PNDM) [72], which has enabled individuals with insulin-dependent PNDM to achieve normal glucose levels with sulfonylurea treatment alone. In contrast, loss of β-cell functional K_{ATP} channel activity has been implicated in the pathogenesis of congenital hyperinsulinism [73], a condition characterized by hypersecretion of insulin. Numerous mutations in both the *Kir6.2* and *SUR1* subunits have been identified in people with congenital hyperinsulinism and these are responsible for the severe impairment in glucose homeostasis in these individuals [74, 75].

Calcium and other intracellular effectors

Intracellular calcium is a principal effector of the nutrient-induced insulin secretory response, linking depolarization with exocytosis of insulin secretory granules (Figure 7.8). A large electrochemical concentration gradient (~10 000-fold) of calcium is maintained across the β-cell plasma membrane by a combination of membrane-associated calcium extruding systems and active calcium sequestration within intracellular organelles. The major route through which calcium is elevated in β cells is by influx of extracellular calcium through voltage-dependent L-type calcium channels that open in response to β-cell depolarization, and it has been estimated that each β cell contains about 500 L-type channels [76].

Studies with permeabilized β cells have demonstrated that elevations in intracellular calcium are alone sufficient to initiate insulin secretion [77], and conditions that elevate intracellular calcium usually stimulate insulin release. An increase in cytosolic calcium is essential for the initiation of insulin secretion by glucose and other nutrients: preventing calcium influx by removal of extracellular calcium or by pharmacological blockade of voltage-dependent calcium channels abolishes nutrient-induced insulin secretion. Glucose and other nutrients also induce a calcium-dependent activation of β-cell phospholipase C (PLC) [78], leading to the generation of inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG), both of which serve second-messenger functions in β cells [79]. The generation of IP_3 leads to the rapid mobilization of intracellular calcium, but the significance of this in secretory responses to nutrients is uncertain, and it is likely to have little more than a modulatory role, amplifying the elevations in cytosolic calcium concentration induced by the influx of extracellular calcium.

The elevations in intracellular calcium are transduced into the regulated secretion of insulin by intracellular calcium-sensing systems within β cells. Important among these are the calcium-dependent protein kinases, which include myosin light-chain kinases, the calcium/phospholipid-dependent kinases, and the calcium/calmodulin-dependent kinases (CaMKs). CaMKs are protein kinases that are activated in the presence of calcium and the calcium-binding protein calmodulin, and several studies have implicated CaMK II in insulin secretory responses [79]. It has been proposed that CaMK II activation is responsible for the initiation of insulin secretion in response to glucose and other nutrients, and for enhancing nutrient-induced secretion in response to receptor agonists that elevate intracellular calcium [79]. Cytosolic PLA_2 ($cPLA_2$) is another β-cell calcium-sensitive enzyme. It is activated by concentrations of calcium that are achieved in stimulated β cells, and it generates arachidonic acid by the hydrolysis of membrane phosphatidylcholine. Arachidonic acid is capable of stimulating insulin secretion in a glucose- and calcium-independent manner, and it is further metabolized in islets by the cyclooxygenase (COX) pathways to produce prostaglandins and thromboxanes, and by the lipoxygenase (LOX) pathways to generate hydroperoxyeicosatetraenoic acids (HPETES), hydroxyeicosatetraenoic acids (HETES), and leukotrienes.

The precise roles of arachidonic acid derivatives in islet function remain uncertain because experimental investigations have relied on COX and LOX inhibitors of poor specificity, and although prostaglandin E_2 is largely inhibitory in rodent islets [80], it has stimulatory effects on insulin secretion from human islets [81]. Calcium sensors are also important at the later stages of the secretory pathway, where the calcium-sensitive synaptotagmin proteins are involved in the formation of the exocytotic SNARE complex, to confer calcium sensitivity on the initiation and rate of exocytotic release of insulin secretory granules [58].

The elevations in intracellular calcium induced by nutrients activate other effector systems in β cells, including PLC and $cPLA_2$, and calcium-sensitive adenylate cyclase isoforms, which generate cAMP from ATP. Although these signalling systems are of undoubted importance in the regulation of β cells by non-nutrients, their role in nutrient-induced insulin secretion is still uncertain. Thus, DAG generated by glucose-induced PLC activation has the potential to activate some protein kinase C (PKC) isoforms. PKC was first identified as a calcium- and phospholipid-sensitive, DAG-activated protein kinase, but some isoforms of PKC require neither calcium nor DAG for activation. The isoforms are classified into three groups:

- Calcium and DAG sensitive (conventional).
- Calcium independent, DAG sensitive (novel).
- Calcium and DAG independent (atypical).

β cells contain conventional, atypical, and novel PKC isoforms [79, 82]. The early literature on the role of PKC in nutrient-induced insulin secretion is confusing, but several studies have shown that glucose-induced insulin secretion is maintained under conditions where DAG-sensitive PKC isoforms are depleted, suggesting that conventional and novel PKC isoforms are not required for insulin secretion in response to glucose [79, 83].

The role of cAMP in the insulin secretory response to nutrients is similarly unclear. cAMP has the potential to influence insulin secretion by the activation of cAMP-dependent protein kinase A (PKA), or via the cAMP-regulated guanine nucleotide exchange factors

known as exchange proteins activated by cAMP (EPACs) [84]. However, elevations in β-cell cyclic AMP do not stimulate insulin secretion at substimulatory glucose concentrations, and the secretagogue effects of glucose can be maintained in the presence of competitive antagonists of cAMP binding to PKA or EPACs [85]. These observations suggest that cAMP does not act as a primary trigger of nutrient-stimulated β-cell secretory function, but observations linking glucose-induced oscillations in β-cell cAMP to oscillations in insulin secretion [86] suggest that a role for this messenger system in nutrient-induced insulin secretion cannot be ruled out.

K_{ATP} channel-independent pathways

Since the early reports linking K_{ATP} channel closure to the exocytotic release of insulin, it has become apparent that β cells also possess a K_{ATP} channel-independent stimulus–secretion coupling pathway: this is termed the amplifying pathway to distinguish it from the triggering pathway that is activated by K_{ATP} channel closure [87]. Studies in which β-cell calcium is elevated by depolarization and K_{ATP} channels are maintained in the open state by diazoxide have indicated that glucose, at concentrations as low as 1–6 mmol/l, is still capable of stimulating insulin secretion [88]. The triggering and amplifying pathways are both physiologically relevant for the first and second phases of glucose-induced insulin secretion [63, 89], but the mechanisms by which glucose stimulates insulin secretion in a K_{ATP} channel-independent manner remain debated, although adenine nucleotides have been implicated [89, 90]. However, it is clear that glucose must be metabolized and various potential metabolic amplifiers of glucose-induced insulin secretion have been identified in experimental studies, with the suggestion that perturbations in these pathways may be involved in β-cell failure in type 2 diabetes [63, 87].

Amino acids

Several amino acids stimulate insulin secretion *in vivo* and *in vitro*. Most require stimulatory concentrations of glucose, but some, such as leucine, lysine, and arginine, can stimulate insulin secretion in the absence of glucose, and therefore qualify as initiators of secretion. Leucine enters islets by a sodium-independent transport system and stimulates a biphasic increase in insulin release. The effects of leucine on β-cell membrane potential, ion fluxes, and insulin secretion are similar to, but smaller than, those of glucose [91]. Thus, metabolism of leucine within β cells decreases the potassium permeability, causing depolarization and activation of L-type calcium channels through which calcium enters the β cells and initiates insulin secretion. Leucine also activates the amplifying pathway of insulin secretion in a K_{ATP} channel-independent manner, as described already for glucose. The charged amino acids lysine and arginine cross the β-cell plasma membrane via a transport system specific for cationic amino acids. It is generally believed that the accumulation of these positively charged molecules directly depolarizes the β-cell membrane, leading to calcium influx.

Regulation of insulin secretion by non-nutrients

The complex mechanisms that have evolved to enable changes in extracellular nutrients to initiate an exocytotic secretory response are confined to islet β cells, and perhaps to a subset of hypothalamic neurons [92]. However, the mechanisms that β cells use to recognize and respond to non-nutrient potentiators of secretion are ubiquitous in mammalian cells, and so are covered only briefly in this section, followed by a review of the physiologically relevant non-nutrient regulators of β-cell function.

Most, if not all, non-nutrient modulators of insulin secretion influence β cells by binding to and activating specific receptors on the extracellular surface. Because of their central role in coordinating whole-body fuel homeostasis, β cells express receptors for a wide range of biologically active peptides, glycoproteins, and neurotransmitters (Table 7.1), and quantitative reverse transcriptase polymerase chain reaction (RT-PCR) analysis has indicated that human islets express 293 different G-protein-coupled receptors [93]. However, receptor occupancy generally results in the activation of a limited number of intracellular effector systems, which were introduced in the section 'Nutrient-Induced Insulin Secretion' (Figures 7.9 and 7.10).

Islet hormones

There is convincing evidence for complex intra-islet interactions via molecules released from islet endocrine cells (Figure 7.2). The physiological relevance of some of these interactions is still debated [40], but some of the intra-islet factors that influence insulin secretion are discussed briefly in this section.

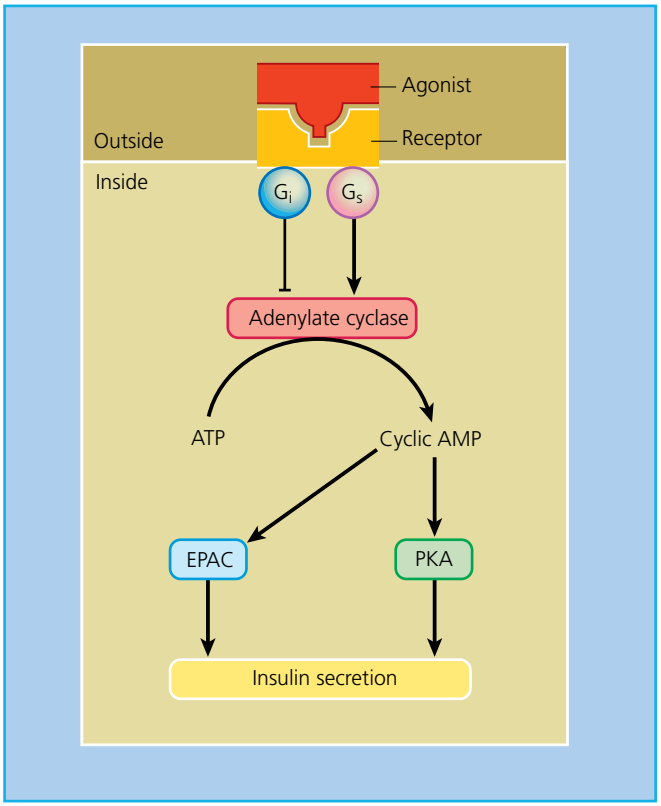

Figure 7.9 Adenylate cyclase and the regulation of insulin secretion. Some receptor agonists (e.g. glucagon, glucagon-like peptide-1, pituitary adenylate cyclase-activating polypeptide) bind to cell-surface receptors that are coupled to adenylate cyclase (AC) via the heterotrimeric GTP-binding protein Gs. Adenylate cyclase hydrolyses adenosine triphosphate (ATP) to generate adenosine 5′ cyclic monophosphate (cAMP), which activates protein kinase A (PKA) and exchange proteins activated by cAMP (EPACs). Both of these pathways potentiate glucose-stimulated insulin secretion. Glucose also activates adenylate cyclase, but increases in intracellular cyclic AMP levels in response to glucose are generally smaller than those obtained with receptor agonists. Some inhibitory agonists (e.g. norepinephrine, somatostatin) bind to receptors that are coupled to adenylate cyclase via the inhibitory GTP-binding protein G_i, resulting in reduced adenylate cyclase activity and a decrease in intracellular cAMP.

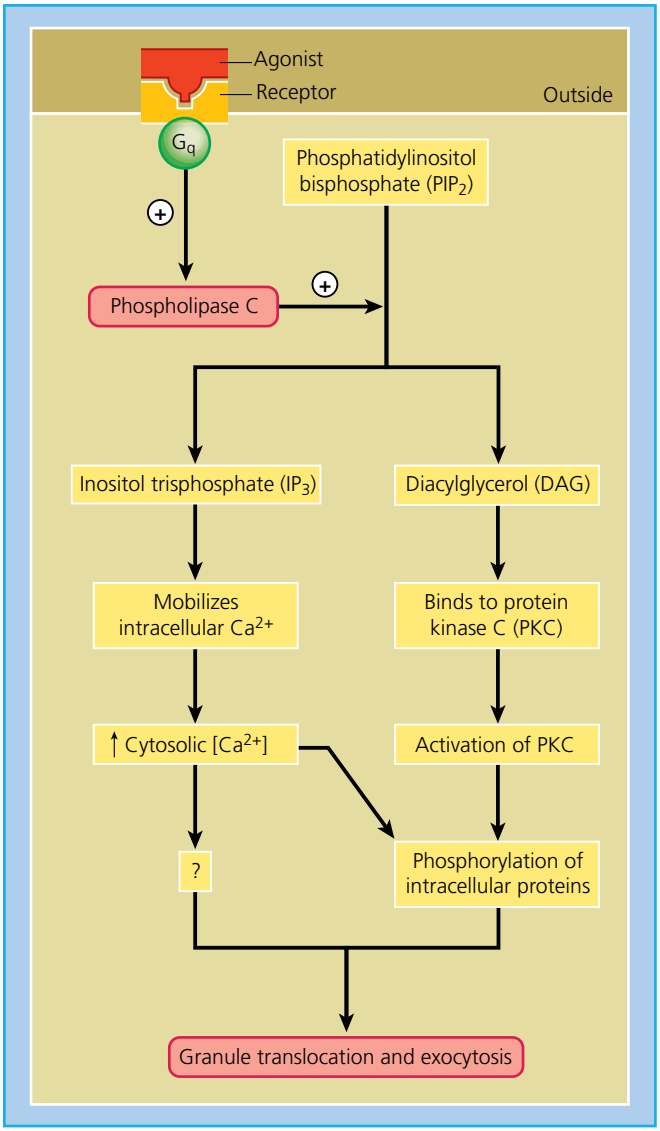

Figure 7.10 Phospholipase C and the regulation of insulin secretion. Some receptor agonists (e.g. acetylcholine, cholecystokinin) bind to cell-surface receptors that are coupled to phospholipase C (PLC) via the heterotrimeric GTP-binding protein G_q. Phospholipase C hydrolyses phosphatidylinositol bisphosphate (PIP_2), an integral component of the membrane, to generate inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 mobilizes calcium from the endoplasmic reticulum and DAG activates protein kinase C (PKC), both of which enhance insulin secretion. Nutrients also activate PLC in a calcium-dependent manner, but the importance of IP_3 and DAG in nutrient-induced insulin secretion is uncertain.

It is clear that β cells express insulin receptors and the associated intracellular signalling elements, suggesting the existence of autocrine and/or paracrine feedback regulation of β-cell function [26, 94]. Earlier suggestions that secreted insulin regulates insulin secretion [95] have not been confirmed [26, 96], and the physiological rationale of a positive feedback loop for insulin to promote further insulin release is questionable [97]. The main autocrine function of insulin on β cells is to regulate β-cell gene expression [98, 99] and β-cell mass through effects on proliferation and apoptosis [26, 99].

Glucagon is a 29 amino acid peptide secreted by islet α cells. The precursor, proglucagon, undergoes differential post-translational processing in the gut to produce entirely different peptides with different receptors and biological activities. These include GLP-1 (7–36) amide, an *incretin* hormone, and GLP-2, which promotes growth of the intestinal mucosa. Although glucagon is the major proglucagon product in islet α cells, a subpopulation of human α cells also synthesizes and secretes GLP-1, presumably to exert local effects within islets [36, 38, 73]. Glucagon secretion is regulated by nutrients, islet and gastrointestinal hormones, and the autonomic nervous system, with hypoglycaemia and sympathetic nervous input being important stimulators of glucagon secretion [100]. Glucagon enhances insulin secretion through the stimulatory G-protein (G_s)–coupled activation of adenylate cyclase and the consequent increase in intracellular cAMP (Figure 7.9).

Somatostatin (SST) is expressed by islet δ cells and in numerous other sites, including the central nervous system (CNS) and D cells of the gastrointestinal tract, where it acts predominantly as an inhibitor of endocrine and exocrine secretion [101]. The precursor, pro-somatostatin, is processed by alternative pathways: in islets and the CNS SST-14 is generated, while SST-28, the major circulating form of somatostatin in humans, is produced in the gastrointestinal tract [102]. Somatostatin secretion is regulated by numerous nutrients and endocrine and neural factors [24, 101, 103, 104]. Islets express five different somatostatin receptor (SSTR) subtypes, and SST-14 released from islet δ cells has a tonic inhibitory effect on insulin and glucagon secretion [24], via activation of SSTR5 and SSTR2, respectively [105, 106]. Somatostatin receptors are coupled via an inhibitory G-protein (Gi) to the inhibition of adenylate cyclase and decreased formation of cAMP [107] (Figure 7.9), and to ion channels that cause hyperpolarization of the β-cell membrane and reductions in intracellular calcium [108]. Live cell imaging studies in rodent and human islets have shown that δ cells possess motile, neural-like processes that enable individual δ cells to reach, and potentially regulate, a large number of β cells within an islet [109].

Pancreatic polypeptide (PP) is a 36 amino acid peptide produced by PP cells that are found in the mantle of islets, predominantly those located in the head of the pancreas. PP secretion is mainly regulated via cholinergic parasympathetic stimulation [110], but the physiological function of PP as a circulating hormone, or as an intra-islet signal, is uncertain [110]. Peptide YY (PYY), which is structurally related to PP, is also expressed in islets, mainly by subpopulations of PP- and δ cells [111]. PYY inhibits insulin secretion via the NPY family of receptors, the most abundant of which is Y1 in both mouse and human islets [93, 112]. Ablation of PYY-expressing cells *in vivo* causes β-cell destruction and induction of diabetes, suggesting a role for islet PYY in maintaining β-cell mass [112].

Ghrelin is a 23 amino acid peptide first identified in the gastrointestinal system, but now known to be expressed in islet ε cells that are localized to the islet mantle in rodents, and appear to be developmentally distinct from the classic islet endocrine cells [113, 114]. The physiological function of ε-cell–derived ghrelin has not been fully established, but most experimental evidence suggests an inhibitory role in the regulation of insulin secretion [115], analogous to that of δ-cell somatostatin [24]. The inhibitory mode of action of ghrelin has been identified as being via GHSR1a receptors, leading to indirect opening of K_{ATP} channels and β-cell membrane hyperpolarization [116]. The recent observations that the ghrelin receptor GHSR shows high co-expression with PP in islets and that its inhibition *in vivo* results in increased circulating PP add another layer of complexity to islet paracrine signalling [117].

Neural control of insulin secretion

The association of nerve fibres with islets was shown over 100 years ago by silver staining techniques [118]. Since that time it has become well established that both mouse and human islets are innervated by cholinergic, adrenergic, and peptidergic autonomic nerves and that the central and autonomic nervous systems are important regulators of islet hormone secretion [8]. Coordination between the brain and the islets is required for normal glucose homeostasis, such that defects in this cooperative system may be associated with the development of type 2 diabetes [8].

The neural pathways regulating autonomic outflow to the islets have been mapped in detail. Parasympathetic (cholinergic) fibres originate in the dorsal motor nucleus of the vagus, while sympathetic nervous system motor neurons (adrenergic) are located in the intermediolateral column of the spinal cord. The activity of both parasympathetic and sympathetic input to islets is regulated by neural input from multiple regions of the hindbrain, midbrain, and forebrain [8].

Neurotransmitters: acetylcholine and norepinephrine

Acetylcholine is the major post-ganglionic parasympathetic neurotransmitter, and it stimulates the release of insulin and glucagon in many mammalian species [7, 93, 119]. Acetylcholine is also synthesized in and secreted from α cells in human islets, where it primes the β cells to respond optimally to increases in glucose [29, 120]. Acetylcholine acts predominantly via M3 receptors in β cells [119, 121] to activate PLC (Figure 7.10), generating IP_3 and DAG, which act to amplify the effects of glucose by elevating cytosolic calcium and activating PKC [77]. Activation of β-cell muscarinic receptors can also lead to PLA_2 activation, with the subsequent generation of arachidonic acid and lysophosphatidylcholine, which can further enhance nutrient-induced insulin secretion. Acetylcholine also depolarizes the plasma membrane by affecting Na^+ conductivity, and this additional depolarization induces sustained increases in cytosolic calcium [119].

The major sympathetic neurotransmitter norepinephrine (noradrenaline) can exert positive and negative influences on hormone secretion. Thus, norepinephrine can exert direct stimulatory effects on β cells via β_2-adrenoreceptors [122], or inhibitory effects via α_2-adrenoreceptors [123], and the net effect of norepinephrine may depend on the relative levels of expression of these receptor subtypes. Differences between species in the expression levels of adrenoreceptor subtypes probably account for the differential effects of β-adrenergic agonists on human islets, where they are stimulatory, and rodent islets, where they are ineffective [124]. The stimulatory effects mediated by β_2-receptors occur by activation of adenylate cyclase and an increase in intracellular cAMP (Figure 7.9), while the inhibitory effect of α_2-receptor activation involves reductions in cAMP and of cytosolic calcium [107, 123], and an unidentified inhibitory action at a more distal point in the stimulus–secretion coupling mechanism [125]. Increased expression of α_2A adrenoreceptors and decreased insulin secretion are a consequence of a SNP in the human α_2A receptor gene [126], and an α_2A receptor antagonist has been used to improve the insulin secretion deficiency in individuals with type 2 diabetes [127]. In contrast to the inhibitory effects of norepinephrine on insulin release, it has direct stimulatory effects on glucagon secretion from α cells mediated by both β_2- and α_2-receptor subtypes [7]. Circulating catecholamines secreted by the adrenal medulla (mainly epinephrine) also have the potential to influence islet hormone secretion through interactions with the adrenoreceptors expressed on the α and β cells.

Neuropeptides

Parasympathetic nerve fibres in islets contain biologically active neuropeptides, including VIP, PACAP, and gastrin-releasing polypeptide (GRP), all of which are released by vagal activation and stimulate the release of insulin and glucagon.

VIP (28 amino acids) and PACAP (27 or 38 amino acids) are abundantly expressed neuropeptides that are widely distributed in parasympathetic nerves that supply the islets and gastrointestinal tract [9]. VIP and PACAP have similar structures, and VIP1 and VIP2 receptors also have an affinity for PACAP. The stimulatory effects of VIP and PACAP on insulin secretion *in vitro* and *in vivo* are through β-cell VIP2 and PAC1 receptors, respectively, and involve increases in intracellular cAMP (Figure 7.9) and cytosolic calcium [9, 128, 129]. GRP is a 27 amino acid peptide that also stimulates the secretion of insulin, glucagon, somatostatin, and PP [7]. These effects of GRP are mediated through specific receptors, and involve the activation of PLC and the generation of IP_3 and DAG (Figure 7.10).

Sympathetic nerves contain different neuropeptides to parasympathetic nerves, including NPY and galanin, both of which have inhibitory actions within islets. NPY (36 amino acids) and galanin (29 amino acids) are expressed in fibres innervating both the endocrine and exocrine pancreas [7, 130]. Both neuropeptides inhibit basal and glucose-stimulated insulin secretion [107, 130, 131], although differences between species have been reported. Both NPY and galanin act through specific G_i-coupled receptors to inhibit adenylate cyclase [93, 132, 133], and galanin may have additional inhibitory effects at an undefined late stage of exocytosis [107].

Regulation of insulin secretion by gut- and adipose-derived factors

Incretins

It has been known for over 50 years that insulin secretion from islets is greater following oral rather than intravenous administration of glucose [134] and it is now known that this enhanced insulin secretory output is a consequence of the release of gastrointestinal-derived *incretin* hormones [135]. The main incretins that have been implicated in an elevated insulin response to absorbed nutrients after food intake are GLP-1, glucose-dependent insulinotropic peptide (GIP), and cholecystokinin (CCK), all of which are hormones secreted by specialized endocrine cells in the gastrointestinal tract in response to nutrient absorption [135, 136]. These hormones are carried to the islets in the blood and they interact with specific receptors on the β-cell surface to stimulate insulin secretion.

Glucagon-like peptide 1

After food intake, L cells of the distal gastrointestinal tract secrete GLP-1 in response to elevated levels of nutrients derived from carbohydrates, lipids, and proteins in the intestinal lumen [135, 136]. GLP-1 is generated by prohormone convertase 1–3 cleavage of proglucagon in the L cells and it is highly conserved in mammals, with identical amino acid sequences in humans and mice [102, 135]. GLP-1 is degraded by dipeptidyl protease 4 (DPP-4), which cleaves two amino acids from its N-terminus. Full-length GLP-1 (1–37) does not show biological activity, but the truncated peptides GLP-1 (7–36) amide and GLP-1 (7–37) are potent stimulators of insulin secretion *in vitro* and *in vivo* [135]. Observations that infusion of the

peptide into individuals with type 2 diabetes before food intake improved insulin output and reduced the post-prandial increase in circulating glucose led to studies to determine whether GLP-1 or related peptides may be useful as therapies for type 2 diabetes. Reports of other beneficial effects of GLP-1, including its capacity to inhibit glucagon secretion, delay gastric emptying, and decrease food intake, indicated its positive effects on normalizing post-prandial glycaemia, but its half-life of less than 2 minutes precludes its use as a diabetes therapy. Nonetheless, exenatide, which is present in the saliva of the Gila monster lizard and has ~50% amino acid homology with GLP-1, has been developed for clinical use for type 2 diabetes [137]. Exenatide exerts the same effects on islets as native GLP-1, but its resistance to degradation by DPP-4 increases its half-life to ~2 hours *in vivo*, which ensures effective regulation of blood glucose levels. Another GLP-1 receptor agonist, liraglutide, has a greatly extended half-life (>12 hours) as a result of incorporation of the fatty acid palmitate into the GLP-1 sequence, allowing it to bind to plasma albumin and reducing its exposure to DPP-4. More recently, an oral GLP-1 receptor agonist formulation (oral semaglutide) has been approved for clinical use [138] and this provides a major advantage over other GLP-1 receptor agonists, which are administered by subcutaneous injection. Selective DPP-4 inhibitors, such as sitagliptin, are used clinically to treat type 2 diabetes by extending the half-life of endogenous GLP-1. GLP-1 and GLP-1 receptor agonists act at islet GLP-1 receptors [93, 135] that are linked, via G_s, to adenylate cyclase activation (Figure 7.9). Elevations in cAMP following GLP-1 receptor activation potentiate glucose-induced insulin secretion via activation of both PKA and EPACs [139]. Improved glucose homeostasis following bariatric gastric bypass surgery results, at least in part, from more rapid delivery of food to the L cells through a shorter gastrointestinal tract, which leads to enhanced post-prandial GLP-1 secretion [140, 141].

Glucose-dependent insulinotropic peptide

GIP, a 42 amino acid peptide, is released from K cells in the duodenum and jejunum in response to the absorption of glucose, other actively transported sugars, amino acids, and long-chain fatty acids [136]. It was originally called *gastric inhibitory polypeptide* because of its inhibitory effects on acid secretion in the stomach, but its main physiological effect is now known to be stimulation of insulin secretion in a glucose-dependent manner [135]. GIP receptors, like those activated by GLP-1, are coupled to G_s, with essentially the same downstream cascades leading to stimulation of insulin secretion (Figure 7.9). Although GLP-1 and GIP both enhance insulin output following their release in response to food intake, development of GIP-related peptide monotherapies for type 2 diabetes is unlikely because GIP stimulates glucagon secretion and inhibits GLP-1 release, and its infusion in individuals with type 2 diabetes worsens post-prandial hyperglycaemia [142]. However, a GLP-1/GIP receptor co-agonist is more effective in normalizing glycaemia and stimulating weight loss in people with type 2 diabetes than a GLP-1 analogue [143], most likely as a consequence of stimulation of GIP receptor signalling pathways in the CNS [144].

Cholecystokinin

CCK is another gastrointestinal hormone that is released from I cells in response to elevated fat and protein levels [136]. It was originally isolated from porcine intestine as a 33 amino acid peptide and the truncated CCK-8 form stimulates insulin secretion *in vitro* and *in vivo* [145]. CCK-8 acts at specific G_q-coupled receptors on β cells to activate PLC (Figure 7.10), and its potentiation of insulin secretion is completely dependent on PKC activation [146]. However, the physiological role of CCK as an incretin has not been established because high concentrations are required for its effects on insulin secretion, and it is possible that its major function in humans is in digestion in the duodenum.

Bile acids

Bile acids act as endocrine factors to enable signalling between the gut and other tissues involved in metabolic homeostasis, including islet cells. They signal via the nuclear receptor farnesoid-X receptor (FXR) and the G-protein–coupled receptor TGR5, both of which are expressed in islets [93, 147]. TGR5 activation stimulates insulin secretion from mouse and human islets *in vitro* [148], but *in vivo* studies using transgenic mice suggest that FXR mediates most, if not all, of the effects of bile acids to enhance insulin secretion [147]. The composition and plasma concentrations of bile acids are altered by gastric bypass surgery, perhaps as a consequence of changes in the gut microbiome, and these changes have been linked to improved β-cell function and metabolic regulation [149]. However, a recent study in which an FXR- and TGR5-activating bile acid and a bile acid sequestrant were delivered to individuals after gastric bypass surgery reported only a limited role for bile acids in acute glucose regulation [150].

Decretins

Starvation studies in humans and other mammals suggest the existence of gut-derived factors that are released post-prandially to suppress insulin secretion and thus prevent post-prandial hyperinsulinaemic hypoglycaemia [151], these factors being referred to as *decretins* [152, 153] or *anti-incretins* [154]. Studies in baboons first identified gut-derived SST-28 as a putative decretin by demonstrating that immunoneutralization of SST-28 caused elevations in post-prandial plasma insulin concentrations [152]. Foregut-derived dopamine has also been proposed as a physiological decretin that is released post-prandially to inhibit glucose- and GLP-1-stimulated insulin secretion [155]. In *Drosophila* the neuropeptide limostatin acts as a decretin by suppressing the activity of insulin-producing cells and reducing the secretion of *Drosophila* insulin-like peptides [153]. The mammalian homologue of limostatin is neuromedin U (NMU), a neuropeptide that is expressed in foregut enteroendocrine cells, and is proposed to act as a decretin by suppressing glucose-induced insulin secretion from human islets through a specific β-cell receptor, NMUR1 [153]. However, intravenous delivery of neuromedin to rats does not affect insulin secretion or blood glucose levels [156]. The same study reported that neuromedin receptors are not expressed by rat or human islets, raising doubts about the decretin status of neuromedin, but NMUR1 has been identified in human islets in another study [93]. While decretins may be important in the pathophysiology of type 2 diabetes [154], most studies have been carried out in rodent models and it is clear that full understanding requires further research, including human clinical studies [157].

Adipokines

Obesity is a risk factor for diabetes, and hormones (adipokines) released from fat depots have been implicated in insulin resistance associated with obesity and type 2 diabetes [158]. Some adipokines, such as leptin, resistin, and adiponectin, are also reported to influence islet function. Thus, β cells express Ob-Rb leptin receptors, which, when activated by leptin, lead to inhibition of insulin secretion [159], and specific deletion of β-cell Ob-Rb receptors is associated with

enhanced insulin secretion [160]. The inhibitory effects of leptin on glucose-stimulated insulin secretion have been attributed to activation of β-cell K_{ATP} channels [161] or of c-Jun N-terminal kinases (JNKs) [162]. Leptin may also further impair β-cell function through reductions in β-cell mass [142, 144]. Resistin, another adipocyte polypeptide, also inhibits glucose-stimulated insulin release [163] and stimulates apoptosis of rat β cells [164], suggesting that it has similar functions to leptin. However, resistin is not considered to be a true adipokine because, although it is secreted at high levels from mouse adipocytes, it is not produced by human adipocytes, and high plasma resistin levels do not correlate with reduced insulin sensitivity [165]. Nevertheless, it is possible that resistin has paracrine effects on β-cell function in humans as it has been identified in human islets [166]. Unlike leptin and resistin, adiponectin has protective effects by improving insulin sensitivity, and decreased plasma adiponectin levels may contribute to the development of type 2 diabetes [167]. Human and rat β cells express AdipoR1 and AdipoR2 adiponectin receptors [168, 169], and adiponectin is reported to stimulate insulin secretion [168, 169], protect against β-cell apoptosis [170], and stimulate β-cell regeneration [171]. The signalling cascades that couple adiponectin receptors to downstream effects in β cells have not been fully defined, but adiponectin is reported to activate the kinases Erk and Akt in islets [172], and it also stimulates expression of genes that regulate lipid transport and metabolism [173]. Other less well-known adipokines, such as adipsin, apelin and chemerin, have also been implicated in improved insulin secretion, via activation of β-cell G-protein–coupled receptors [174].

Conclusions

Islets of Langerhans are complex micro-organs containing different types of endocrine cells, with extensive vasculature and autonomic nerve supply. Interactions between the islet cells, the autonomic and central nervous systems, and hormones secreted by the gastrointestinal system and adipose tissue permit the appropriate release of islet hormones to regulate metabolic fuel usage and storage.

The insulin-secreting β cells within islets respond to changes in circulating nutrients by linking changes in nutrient metabolism to β-cell depolarization and the calcium-dependent exocytotic release of stored insulin. Islet β cells can also respond to a wide range of hormones and neurotransmitters through conventional cell-surface receptors that are linked to intracellular effector systems regulating the release of insulin. The ability to detect nutrient, hormonal, and neural signals allows β cells to integrate information about the prevailing metabolic status, and to secrete insulin as required for glucose homeostasis.

This detailed understanding of islet cell biology has informed the development of new treatments for type 2 diabetes, such as GLP-1 receptor agonists and DPP-4 inhibitors. It is now acknowledged that β-cell dysregulation is a key factor in the development of type 2 diabetes. Advances in our understanding of normal β-cell function may therefore assist in identifying the β-cell pathologies in type 2 diabetes, and in developing new therapeutic approaches.

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8 Glucagon in Islet and Metabolic Regulation

Jonathan E. Campbell and David A. D'Alessio
Department of Medicine, Division of Endocrinology, Duke University, Durham, NC, USA

Key points

- Glucagon is made predominantly in islet α cells and regulates systemic glycaemia through actions in the liver and islet β cell.
- Glucagon has direct actions on hepatocytes to promote glucose production, lipid metabolism, and amino acid metabolism.
- Hepatic glucagon signalling is essential for normal amino acid metabolism and increased circulating amino acids stimulate α-cell glucagon production.
- Excess glucagon contributes to dysglycaemia in some people with diabetes and may contribute to diabetic ketoacidosis in those with type 1 diabetes.
- Compounds that both stimulate and antagonize the glucagon receptor are under investigation for treatment of metabolic disorders.

Glucagon is a regulatory peptide made almost exclusively in the α cells of the pancreatic islet and has a notable history in basic research, clinical physiology, and therapeutics. Discovered initially as a contaminant in the process of insulin extraction from the pancreas [1], the demonstration of specific actions to raise blood glucose led to a physiological model in which glucagon acted as a counterbalance to insulin, providing glucose under circumstances of need [2]. The fundamental aspects of glucagon signalling at the cellular level formed much of the basis for the discovery of cyclic adenosine monophosphate (cAMP) and G-proteins [3]. Glucagon was one of the first hormones that could be measured in the circulation and tissues of humans and experimental animals. Early work demonstrated dramatic increases in circulating levels with hypoglycaemia and extreme physical exertion [2], and smaller but consistent elevations during starvation [4]. Especially important was the observation that glucagon levels were elevated in many people with diabetes, dramatically so during diabetic ketoacidosis [5,6]. These findings raised the possibility that both islet hormones, insulin and glucagon, had a role in the pathogenesis of diabetes [7], a hypothesis that was supported by human experiments using somatostatin to inhibit α-cell secretion [8]. Interest in glucagon as a central factor in diabetes pathophysiology waned for several decades as the focus of metabolic research and treatment of diabetes focused on insulin resistance and defects in β-cell function. However, recently glucagon has regained its status as a topic of great interest in diabetes investigation, and renewed attention to glucagon physiology has been bolstered by the advent of new drugs that suppress glucagon as part of their glucose-lowering activity.

This chapter will review basic concepts in α-cell biology and glucagon physiology with an emphasis on how these processes are altered in disease states, particularly diabetes. Relatively new findings that implicate glucagon in intra-islet signalling, hepatic protein metabolism, and energy balance, as well as descriptions of new uses for glucagon activity in drug development, will be discussed. The role of glucagon in hypoglycaemic counter-regulation is addressed in detail in Chapter 40 and will not be considered in depth here. The pharmacology of available diabetes drugs that affect glucagon secretion, such as dipeptidyl-peptidase inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists, is covered in Chapter 36. There are several recent reviews that cover the molecular and systemic physiology of glucose in more detail than the current chapter [9–12].

Anatomy and development of α cells

The function of glucagon and other α-cell products is based in great part on the anatomy of the pancreatic islet. New research implicates the α cell in paracrine regulation of the endocrine pancreas, and islet structure has an important bearing on this function. Recent studies demonstrating key differences in islet architecture between rodents and humans have provided new insights into pancreatic endocrine function. These differences include heterogeneity of islet size and organization within species [13,14]. In mice and rats the organization of the islet includes a mantle of α and δ cells on the periphery of the islet, surrounding a core of β cells (Figure 8.1). Estimates of the relative endocrine cell composition in rodent islets are ~75–80% β and 20–15% α cells, and most β cells have contact with other β cells [15–17]. In humans, the major endocrine cell types are spread more diffusely throughout the islet, most β cells have contact with either α or δ cells, and the percentage of β cells per islet is 40–60% (Figure 8.1) [13–15]. Based on recent analyses of large numbers of human pancreata, the frequency of contacts between α and β cells appears to be much greater than previously estimated, as is the

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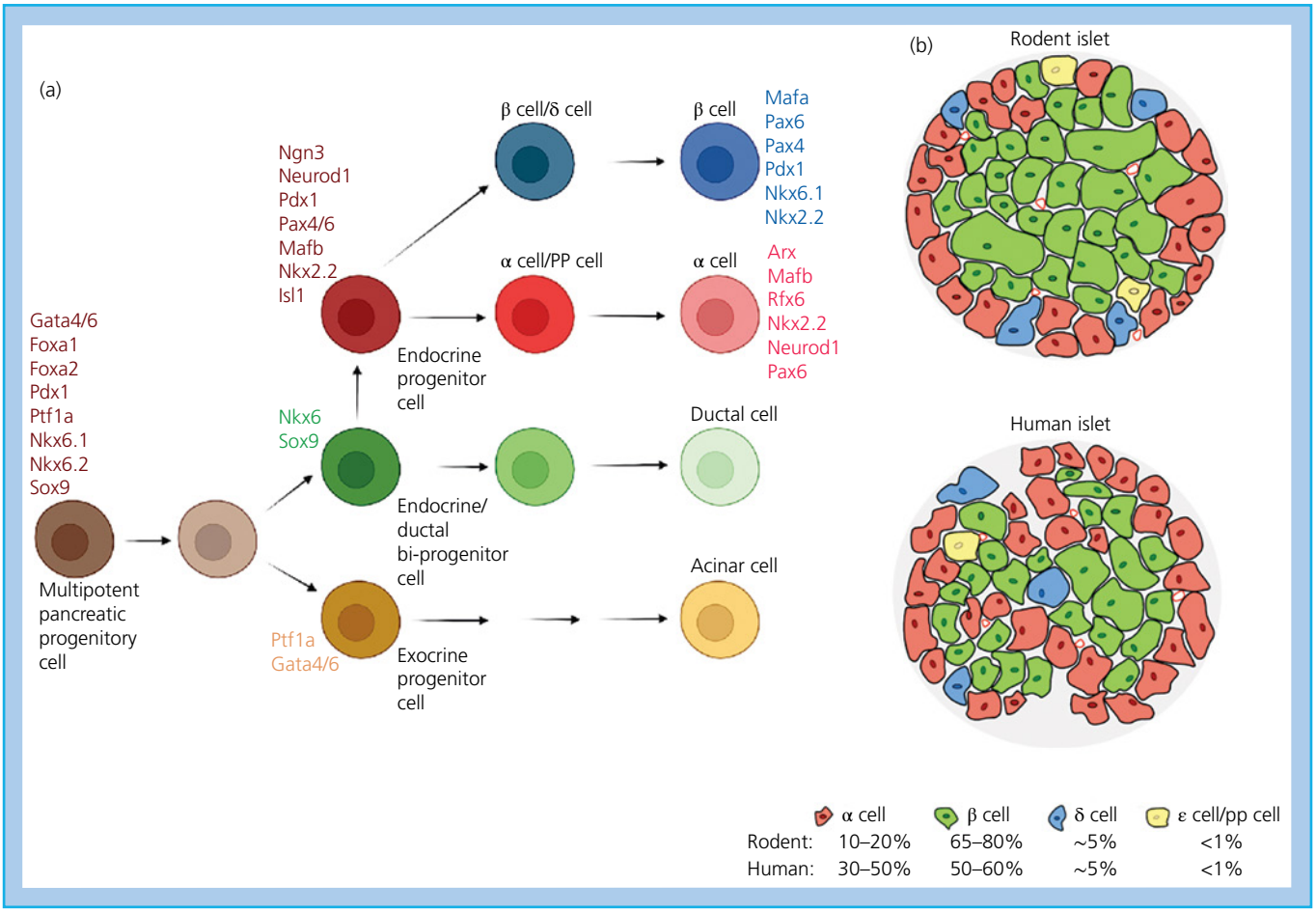

Figure 8.1 Islet development and composition. (a) Cellular markers for pancreatic exocrine and endocrine cell types through development. (b) Cell populations of endocrine cells in pancreatic islets from rodents versus humans. Human islets contain a higher percentage of α cells, with more α cells in the centre of the islet. Rodent islets have fewer α cells that are primarily found on the outside of the islet.

location of islet endocrine cells in close proximity to the microvasculature [13]. In humans, smaller islets have cellular architecture that resembles rodents – that is, a ring of α cells surrounding a β-cell core with a higher percentage of β cells than larger islets; smaller islets also have greater relative insulin secretion [13,14]. These recent studies on the organization of islet anatomy, particularly in humans, have shifted the focus from interactions mediated through the microcirculation to control through direct cell-to-cell contacts.

Neural regulation of islet function is well established, although the nature and magnitude of effects are still under debate. In general, sympathetic nervous system activity is thought to be important in settings where there is enhanced demand for glucose – that is, hypoglycaemia and physical activity – and parasympathetic activity is important before and during meal ingestion [18–20]. Recent data suggest a difference between the density of autonomic innervation of rodent and human α and β cells, with rats and mice having greater density of neural fibres in islets [21]. While this has led to the hypothesis that neural regulation of islet secretion is more important in rodents and paracrine control in humans, this has not been formally tested, and not all studies have demonstrated reduced innervation of human islet cells [22].

The formation of α cells is within the general process of pancreatic development in early embryonic life, directed by the sequential and interacting effects of specific transcription factors (Figure 8.1). Most of the current knowledge on endocrine pancreatic development comes from studies in mice, and while there are general similarities with human islet development, some key differences exist [23–25]. In both mice and humans, pancreatic duodenal homeobox 1 (Pdx1) directs the differentiation of pancreatic epithelial cells, which will become the exocrine and endocrine pancreas, from the foregut endoderm [26]. Subsequent expression of neurogenin 3 (Ngn3) initiates the primary differentiation of endocrine precursors and their initial association into discrete cellular aggregates. The transcription factor aristaless-related homeobox (Arx) is critical for determining a definitive α-cell fate for developing endocrine progenitors, and in its absence normal α cells do not develop [27]. Both mice and humans also have a secondary transition of endocrine development where the various hormone-producing cells start to express the gene profiles that mark mature endocrine cells [26,27]. In mice, glucagon-producing cells are the first detectable endocrine cell type, while insulin-containing cells are the earliest form in humans [25]. Once the secondary transition has occurred, the formation of islets in the distinct murine and human forms progresses throughout the remainder of the prenatal period [24]. The molecular physiology of islet development has assumed particular importance as efforts progress to generate β cells for potential use in therapeutics. There is evidence that mature α cells can be reprogrammed to insulin-producing cells in

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states of severe β-cell loss [28], and that diabetes induces dedifferentiation of β cells into α cells [29]. The plasticity of islet cells is only beginning to be understood, but holds promise for understanding the mechanisms of various forms of diabetes.

Proglucagon gene transcription, translation, and peptide processing

Pre-proglucagon (*Gcg*), the gene that encodes glucagon, is expressed in pancreatic islet α cells but also within the hindbrain, specifically in a subset of neurons in the nucleus of the solitary tract, and within the enteroendocrine L-cell of the intestinal mucosa [30,31]. Regulation of *Gcg* expression is complex, but initiating signals include elevations of cAMP and/or amino acids, and the effects of several specific transcription factors [32–34]. *Gcg* expression is differentially regulated in the pancreas and intestine. The most relevant example of this is related to nutritional state, with fasting increasing islet *Gcg* expression, while feeding promotes transcription in L cells [35]. As an extension of this level of regulation, insulin inhibits *Gcg* transcription in islet α cells [33,36], but increases *Gcg* expression in intestinal endocrine cells [37,38]. The latter effect is mediated in part by signalling related to transcription factor 7 like 2 (TCF7L2), a gene product linked to type 2 diabetes in genetic epidemiological studies [39], which seems to be specific for control of L-cell *Gcg* transcription [37]. Bowel resection or injury causes a large increase in intestinal *Gcg* expression [40]. Differential regulation of *Gcg* transcription in intestinal and islet endocrine cells is in keeping with their distinct patterns of prohormone processing and the predominant secretion of glucagon from the pancreas and GLP-1 and GLP-2 by the gut.

The differential synthesis and release of *Gcg* peptides from α cells compared to intestinal and neural cells expressing *Gcg* is the result of tissue-specific post-translational modification by prohormone convertases (PC). In the α cell, PC2 is the major convertase and it cleaves specific sites along proglucagon to release glucagon, but not the glucagon-related peptides [41]. In contrast, intestinal L cells have significantly more PC1/3 than PC2 activity, and process proglucagon into GLP-1, oxyntomodulin, and GLP-2 as physiologically relevant products [42–44]. There is PC1/3 expression in α cells, albeit at lower levels than PC2, and increasing evidence for islet production of GLP-1; similarly, there have been reports of glucagon produced from enteroendocrine cells in individuals after bariatric surgery [45]. While PC2 is expressed by some central nervous system (CNS) neurons, it is not co-localized with *Gcg*, and only trace amounts of glucagon have been detected in the CNS [42]. In addition to glucagon and the glucagon-like peptides, other proglucagon-derived peptides are measurable in tissue extracts and the circulation and may have signalling properties. These include oxyntomodulin, glicentin, glicentin-related pancreatic polypeptide (GRPP), major proglucagon fragment (MPGF), and mini-glucagon [12].

Regulation of α-cell secretion

Glucagon is the chief secretory product of α cells and glucagon concentrations have been used as the principal measure of α-cell function *in vivo* and *in vitro*. With the possible exception of individuals treated with bariatric surgery [45], there is no evidence that tissues besides the islet α cell release glucagon into the circulation. Glucagon secreted from islets in the pancreas collects in the portal vein, where concentrations are higher than other major vascular systems, and the liver is the primary target of glucagon signalling. Circulating glucagon is cleared by the liver and kidney, with roughly equal contributions by each organ, and 20–40% hepatic clearance of portal venous content [46–48]. Glucagon secretion is regulated by a complex interplay of nutrient, endocrine, paracrine, and neural factors (Figure 8.2). While there is convincing evidence to support this diverse control of α-cell secretion, how the system is integrated varies under different physiological states, and is altered by disease in ways that are still not well understood.

Like the β-cell secretion of insulin, ambient glucose concentrations also regulate α-cell release of glucagon. Low glucose levels increase and high concentrations inhibit glucagon secretion, in part through changes in α-cell electrical activity involving K_{ATP} channels [49–51]. It remains a curiosity that α and β cells have similarities in key aspects of glucose transport, metabolism, and K_{ATP} channel activity, yet opposite secretory responses to changes in ambient glucose. Differences in resting electrical characteristics and ion channel function downstream of K_{ATP} channel closure can explain much of the reciprocal pattern of glucagon and insulin secretion at relative hypo- and hyperglycaemia [51–53]. Moreover, new findings suggest that α cells, but not β cells, express sodium glucose transporters (SGLTs) 1 and 2 [54], and that reduced flux through SGLT-2 increases glucagon secretion. It is unclear how SGLT function is integrated with other aspects of α-cell glucose metabolism, but observations that humans treated with SGLT-2 inhibitors have increased plasma glucagon suggests that this is an active physiological mechanism [55,56]. Beyond glucose, amino acids are another nutrient source that stimulates α cells. Protein meals or infusions of amino acids stimulate glucagon release, and arginine is commonly used to stimulate glucagon secretion in research studies. Among the amino acids alanine, glutamine, proline, and glycine are also potent α-cell secretagogues [57,58].

Substantial differences exist between glucagon release from isolated α cells and intact islets [10,59,60], suggesting that other islet cells have important roles in α-cell regulation. Endocrine cells in islets are exposed to high concentrations of local products and both insulin and somatostatin inhibit glucagon release [10], acting either through the microvasculature or by local cell-to-cell contact. Insulin contributes measurably to the suppression of glucagon after meals [61] and during progressive hyperglycaemia [62]. Other compounds released from β cells inhibit glucagon release, including zinc [59], γ-amino-butyric acid [63], and glutamate [10], but the physiological relevance of these compounds is unclear. Exogenous somatostatin is a potent inhibitor of glucagon secretion [64], and somatostatin secreted from islet δ cells restrains α-cell secretion during exposure to circulating nutrients after meals. A final mechanism of intra-islet regulation of glucagon is autocrine, as recent work suggests that other α-cell products may regulate the α cells. The α cells from both primates and mice secrete glutamate and express ionotropic glutamate receptors (iGlutR) [65]. Glutamate stimulates glucagon release, and this seems to be important for the normal response to low plasma glucose, since inhibition of iGlutR impairs hypoglycaemic counter-regulation in mice [65].

The autonomic nervous system is critical for the regulation of glucagon secretion, particularly in the setting of hypoglycaemic counter-regulation. Activation of both the parasympathetic and sympathetic limbs of the autonomic nervous system increases glucagon release [19], and adrenal epinephrine has a similar effect that may be especially important when blood glucose is very low.

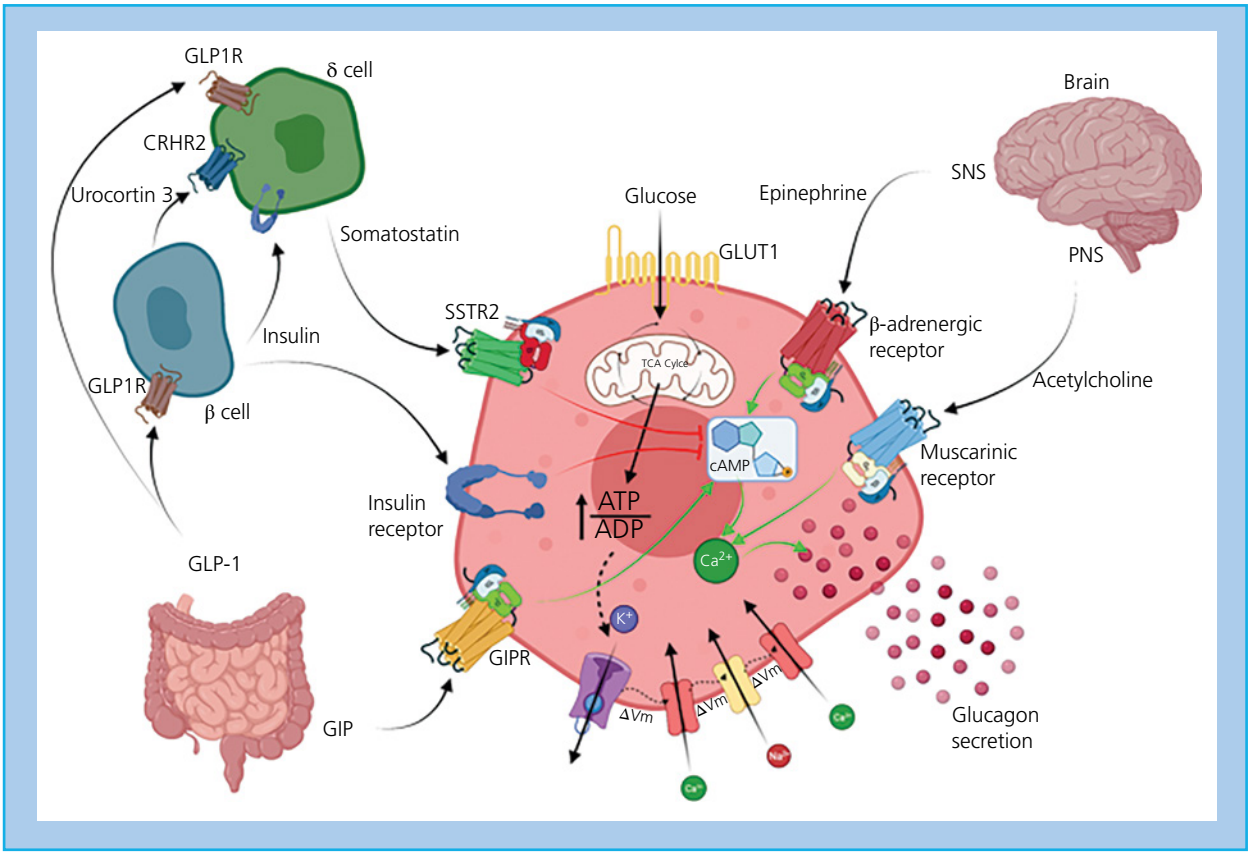

Figure 8.2 Signals that integrate to regulate α-cell secretion of glucagon. The α cell receives input from multiple sources including neuronal, endocrine, and paracrine signals. The incretins are endocrine signals that regulate α-cell function both directly (GIP) and indirectly (GLP-1). Paracrine signals within the islet originate from both the β cell and the δ cell. Activation of the β cell enhances these paracrine signals, directly inhibiting the α cell through factors such as insulin, γ-aminobutyric acid, or Zn^{2+}, and indirectly by increase δ-cell activity through the urocortin 3 system. Increased activity of the δ cell inhibits glucagon secretion through somatostatin. The α cell also receives neuronal input through the sympathetic (SNS) and parasympathetic nervous systems (PNS), both of which increase glucagon secretion. CRHR2, corticotropin-releasing hormone receptor 2; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; SSTR2, somatostatin receptor 2.

Importantly, catecholaminergic signalling synergizes with low blood glucose to stimulate glucagon release [53], and genetic disruption of autonomic neurons in the islet predisposes mice to hypoglycaemia [66]. The key regions in the CNS for sensing circulating blood glucose and initiating counter-regulation are located in the hypothalamus and hindbrain [67,68].

Similar to insulin, glucagon release is also affected by the actions of enteric peptides [10,69]. Glucose-dependent insulinotropic polypeptide (GIP) stimulates glucagon release through direct actions on the GIP receptor expressed on α cells [70]. It is of great importance that the other major *Gcg* peptide, GLP-1, inhibits glucagon secretion, although there is debate over the mechanism whereby this occurs, since the majority of α cells do not express the GLP-1 receptor [71]. GLP-1 increases the secretion of hormones from both β and δ cells, and so could act indirectly to reduce glucagon release [10,69], and this is currently considered to be the primary means by which GLP-1 acts on the α cell. In addition, GLP-1 affects electrical activity and secretion of α cells, even in the absence of changes in somatostatin or insulin [72].

Overall α-cell regulation is a complex, multilayered process with dense integration of control by nutrients and neural, endocrine, paracrine, and autocrine inputs to secretion. Because glucagon has a key role across a range of physiological settings, during fasting, exercise, hypoglycaemia, and following mixed-nutrient meals, α cells are subject to a diversity of controlling factors. While there appears to be some overlap in α-cell control, it seems likely that some regulatory factors also have specific roles as well. Further understanding the regulation of glucagon secretion, and adaptation of therapeutic approaches to control this process, has great potential for the treatment of metabolic disease.

Glucagon actions in the liver: glucose and lipid metabolism

Glucagon action is mediated by the glucagon receptor (GCGR), a family B G-protein–coupled receptor that is highly conserved across mammalian species [73]. Binding of glucagon to the GCGR activates adenylyl cyclase through the G_s subtype G-protein generating cAMP and activating protein kinase A (PKA) as one major mode of intracellular signalling [74]. However, the GCGR also couples to Gq, suggesting access to a wider range of downstream signalling pathways [75,76]. The richest source of glucagon binding is in the liver and kidney; lesser binding occurs in heart, adipose tissue, the CNS, adrenal gland, and spleen [73]. Consistent with the relative receptor expression, the liver and kidney play the major role in glucagon clearance, accounting for ~70% of the removal from the circulation [46,48,73]. The half-life of glucagon in circulating plasma is relatively short: 2, 5, and 7 minutes in rats, dogs, and humans, respectively [73,77].

The first known action of glucagon, to increase hepatic glucose production, was recognized nearly 100 years ago [3]. Subsequent work demonstrated effects of glucagon to counter hypoglycaemia and led to the general principle that it has a role opposing that of insulin to maintain plasma glucose in times of stress, fasting, or exercise [3]. The endocrine mechanism of glucagon action is based on the effects of exogenous glucagon to increase hepatic glucose output in animals, humans, and several *in vitro* systems, as well as the observation that removal of circulating glucagon with a neutralizing antibody reduces blood glucose [77,78].

The cAMP/PKA signalling pathway is critical for the ability of glucagon to regulate hepatic glucose production [77,79]. The downstream activation of phosphorylase kinase and its target glycogen phosphorylase activates glycogenolysis and inhibits glycogenesis [80,81]. However, insulin also regulates these pathways. Thus, a long-held view is that the balance between glycogen breakdown and synthesis results from the relative insulin and glucagon effects on hepatocytes, the degree of cAMP signalling, and the level of glycogen stores [81]. Strategies that increase glycogen synthesis relative to glycogenolysis promote glucose tolerance [80,82] and are potential therapeutic targets for hyperglycaemia. GCGR signalling also regulates the flux between glucose-6-phosphate and fructose bisphosphate via action on fructose 2,6 bisphosphatase and its inhibition of pyruvate kinase activity [77]. The result of cAMP signalling is rapid inhibition of hepatic glucose metabolism and mobilization of stored glucose to deliver glucose to peripheral tissues.

However, another critical aspect of glucagon-induced regulation of hepatic glucose production is through enhancement of the gluconeogenic pathway, an action mediated by PKA activation of CREB and Forkhead box (FOXO1). Glucagon upregulates phosphoenolpyruvate carboxykinase (*Pepck*) gene transcription, which varies with the metabolic state, increasing during fasting and decreasing in response to insulin [77]. PEPCK catalyses a key step in gluconeogenesis by converting oxaloacetate, a product of the tricarboxylic acid (TCA) cycle, into phosphoenolpyruvate. In animal models, gluconeogenesis is increased by overexpression of *Pepck* [83] and conversely decreased by deletion of *Pepck* [84,85]. Other key genes involved in glucose production, including peroxisome proliferator-activated receptor-γ coactivator 1 (*PGC-1*) and glucose-6-phosphatase (*G6P*), are also activated by glucagon signalling. Overall, glucagon regulates several processes within the gluconeogenic pathway that enable sustained glucose production, an effect that is enhanced in the face of limited glycogen supply. Gluconeogenesis is an energy-demanding process, requiring six moles of high-energy phosphate bonds for each mole of glucose produced, and is tightly linked to TCA cycle activity and lipid oxidation for sources of ATP [84]. Indeed, glucagon contributes to hepatic fatty acid oxidation and ketogenesis at several metabolic steps [86,87], and elimination of glucagon action increases liver triglyceride content during fasting. A recent study has shown the centrality of the inositol triphosphate receptor 1 to mediate fatty acid mobilization and oxidation downstream of the GCGR [88]. Taken with previous work, these new findings support a model whereby glucagon has broad effects on hepatic fuel metabolism, generating energy from lipids to support glucose production.

The effects of glucagon on hepatic glucose and lipid metabolism may also lead to pathological consequences if they are not counterbalanced by appropriate levels of insulin action. Increased glucagon during extended periods of fasting or uncontrolled type 1 diabetes stimulates fatty acid oxidation and contributes to ketogenesis [9]. The transcription factor FOXA2 may play a central role in this process. FOXA2 controls the expression of genes involved in fatty acid oxidation and ketogenesis [89,90] and is activated by both fasting and glucagon. Insulin has opposing effects on FOXA2 [91], presenting yet another example of coordinated and inverse regulation by insulin and glucagon on glucose and lipid metabolism, with glucagon more active in the fasted state and insulin predominating during and after feeding.

Studies in humans using somatostatin to inhibit insulin and glucagon secretion, with selective replacement of one or both hormones, are consistent with the knowledge gained from preclinical animal studies. Glucagon is necessary to support normal fasting glucose levels [92,93] and basal insulin replacement without glucagon results in hypoglycaemia. However, physiological regulation of hepatic glucose production by glucagon occurs against a backdrop of constant but variable hepatic insulin action [94]. At glucose levels of 4.5–5.5 mmol/l, plasma glucagon levels are relatively low and unchanging, while changes in glycaemia within this range can affect insulin secretion. This suggests that the effect of glucagon to promote glycogenolysis and initiate gluconeogenesis during fasting occurs tonically, with the absolute level of fasting blood glucose determined by variations of hepatic insulin action. At a cellular level, this can be conceived as glucagon maintaining a threshold of cAMP, or other signalling mediators, that can be modulated by changes in hepatic insulin signalling.

Although glucagon-driven hepatic glucose production includes both glycogenolysis and gluconeogenesis, these two processes follow different temporal patterns. As fasting progresses, the contribution of glycogenolysis to total hepatic glucose output wanes such that glycogenolysis contributes ~50% of liver glucose output in the postabsorptive state but less than 10% after 36 hours of fasting [95,96]. In acute experiments, where glucagon action can be selectively increased, glycogenolytic effects predominate [97]. This is because activation of gluconeogenesis by glucagon requires a supply of glucose precursors, primarily lactate, alanine, and glycerol. Increased delivery of these compounds to the liver is not directly regulated by glucagon and requires a longer period of fasting to reduce plasma insulin and disinhibit lipolysis and proteolysis. With extended periods of starvation, gluconeogenesis becomes even more tightly controlled by precursor supply as preservation of protein stores becomes essential [98].

The hallmark of glucagon action in homeostasis is to increase hepatic glucose production during hypoglycaemic counterregulation (Figure 8.3) [99]. Glycogenolysis provides the most rapid source of glucose. However, the rise in catecholamines that also occurs with hypoglycaemia provides a supply of glucose precursors for gluconeogenesis as well as direct stimulation of hepatic glucose production through hepatic adrenergic receptors [100]. Thus, there is an integrated, synergistic effect of catecholamines and hypoglycaemia to stimulate glucagon release and glucagon action to return glucose levels to normal.

Glucagon also contributes to the maintenance of blood glucose during exercise, another metabolic stressor [101,102]. Similar to hypoglycaemia, increasing catecholamines and glucagon in response to exercise, combined with the usually low circulating levels of insulin, enhance glucagon action and ensure adequate glucose output to maintain glucose supply to peripheral working muscles. With prolonged exercise, the impact of glucagon to promote lipid oxidation becomes increasingly important to preserve limited glucose and provide energy [103].

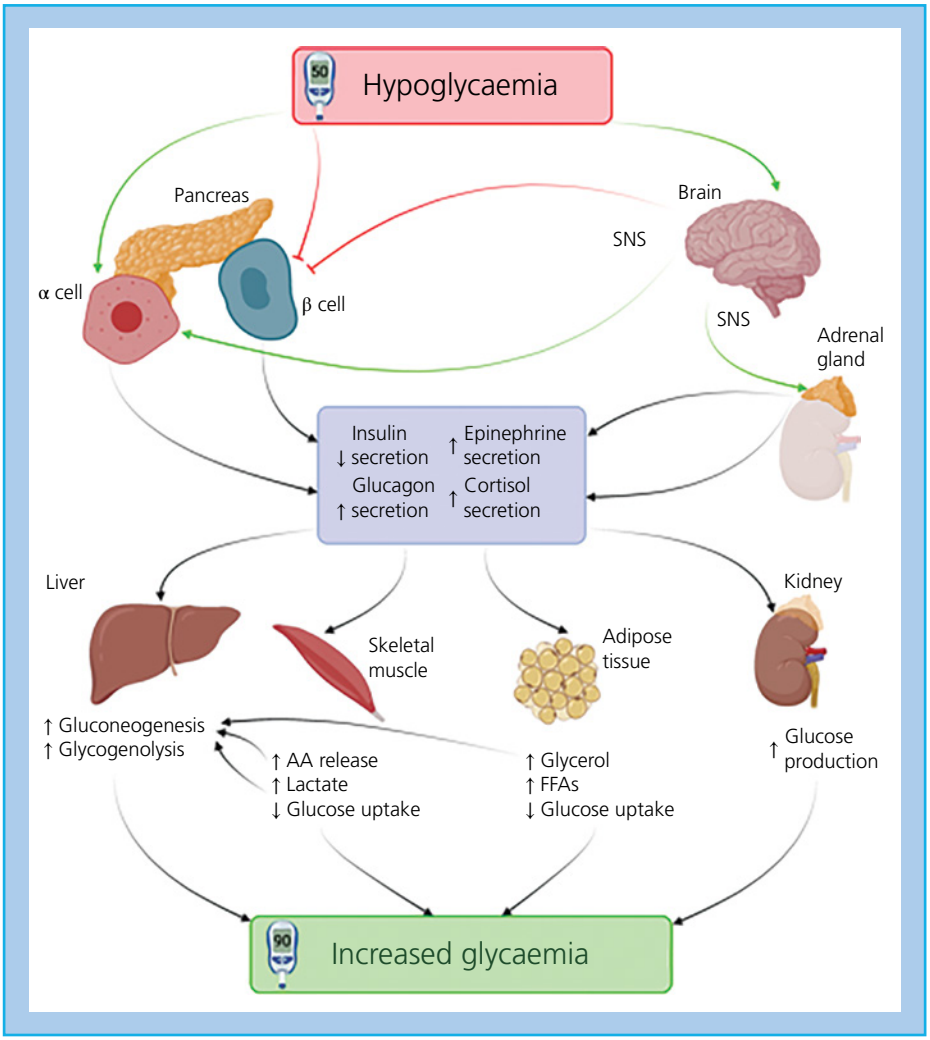

Figure 8.3 Counter-regulatory actions in response to hypoglycaemia. A decrease in glycaemia initiates multiple events in order to restore euglycaemia. In the islet, a low blood glucose decreases insulin secretion from β cells and increases glucagon secretion from α cells. Hypoglycaemia also initiates neuronal sympathetic tone, which increases glucagon, cortisol, and epinephrine secretion. The changes in hormone concentrations in response to hypoglycaemia are summarized in the middle of the figure. These hormonal changes increase glycaemia by enhancement of glucose production by the liver and kidney, reduction of glucose uptake into peripheral tissues, and efflux of amino acids (AAs) and lipid products from skeletal muscle and adipose tissue, respectively. The increased concentrations of AAs, lactate, and glycerol facilitate gluconeogenesis to further increase hepatic glucose output. AA, amino acid; FFA, free fatty acid; SNS, sympathetic nervous system.

Although the physiology of glucagon to regulate hepatic glucose and lipid metabolism is based on a large base of experimental evidence accumulated over many years, several recent reports have raised questions about the fundamental aspects of the consensus model. The pre-eminence of G_s/cAMP signalling as the basis for driving hepatic glucose production has been challenged by preclinical studies that implicate signalling through G_i as increasing glycogenolysis and gluconeogenesis [104]. A similar challenge to traditional thinking is based on studies in mice showing that glucagon is dispensable for the ketosis induced by starvation or SGLT-2 inhibitor treatment [105]. Finally, an effect of hepatic glucagon receptor signalling to improve insulin-stimulated glucose uptake in skeletal muscle and brown fat has been described in mice [106], suggesting a broader role for glucagon on glucose disposition through indirect mechanisms. These findings suggest that there remain significant gaps in understanding glucagon action, and that further study could provide insights into disease and potential for therapeutic development.

Glucagon actions in the liver: amino acid metabolism and the hepatic–α-cell axis

Glucagon plays an important role in amino acid metabolism, and experimental variation of circulating glucagon across the physiological range causes inverse changes of plasma concentrations of amino acids in humans [107, 108]. This effect is most pronounced for glucogenic amino acids [108], and is associated with increased urinary excretion of nitrogen [107] and enhanced glucose production [107, 108], supporting a link between glucagon-induced amino acid catabolism and gluconeogenesis. In mice, genetic deletion of the GCGR, or its antagonism with a blocking antibody, causes downregulation of genes encoding proteins involved in amino acid catabolism and the urea cycle, and an increase in circulating amino acids [109]. Acute blockade of the GCGR caused an almost immediate increase in circulating glucagon, and induced α-cell hyperplasia within several days. A profound increase in islet α cells along

with hyperaminoacidaemia and hyperglucagonaemia are cardinal features of mice with genetic deletion of GCGR; each of these abnormalities is at least partially corrected with liver-specific re-expression of GCGR [109]. Considered together, findings from studies of humans and mice suggest a physiological connection between the liver and α cell mediated by amino acids.

Understanding of the liver–α-cell axis has become an area of active investigation. Recently two groups independently reported the importance of the amino acid transporter Slc38a5 for mediating amino acid–induced hyperplasia of α cells [110, 111]. This specific transporter actively transports several amino acids into α cells, including glutamine, alanine, and glycine, three prevalent species that increase markedly with interruption of glucagon signalling to the liver. Expression of Slc38a5 is increased with GCGR blockade or deletion and is necessary for the full manifestation of α-cell hyperplasia in these settings. L-glutamine seems to be the key amino acid driving α-cell hyperplasia [110], a process that is dependent on mechanistic target of rapamycin (mTOR) signalling [109–111], a fundamental pathway connecting energy and amino acid availability with cell growth.

The liver–α-cell axis may be involved in the pathogenesis of metabolic liver disease and type 2 diabetes. Individuals with obesity and greater hepatic steatosis than lean individuals had hyperaminoacidaemia, hyperglucagonaemia, and downregulation of hepatic expression of genes involved in amino acid transport and metabolism [112]. When given infusions of exogenous glucagon, circulating amino acids were reduced in lean individuals but not those with obesity. Based on these results, as well as supporting findings that people with non-alcoholic fatty liver disease (NAFLD) have increased plasma levels of glucagon and amino acids, it has been proposed that impairment of the liver–α-cell axis may link hepatic steatosis and dysregulated glucose metabolism [113].

Glucagon intra-islet communication and insulin secretion

The GCGR is expressed by islet β cells and supraphysiological amounts of glucagon stimulate insulin release *in vitro* and *in vivo* [114–116]. In isolated human and rat islets studied in culture, antagonism of the GCGR impairs insulin secretion in response to increased media glucose, suggesting a physiological role for islet glucagon action to maintain normal β-cell stimulus–secretion coupling [77, 80, 81]. Consistent with local control of insulin secretion mediated by α-cell products, dispersed β cells are more responsive to glucose when attached to an α cell [117]. Thus, paracrine regulation mediated by α-to-β-cell communication (Figure 8.4) is increasingly accepted and has gained additional support from recent studies. Several groups, using complementary approaches, have shown that glucagon acts through both glucagon and GLP-1 receptors on β cells to stimulate insulin release [116, 118, 119], an effect that is apparent in both mouse and human islets [57]. One proposed effect of α-cell products on systemic homeostasis is regulation of the glycaemic set-point – that is, the normal basal concentration of blood glucose – through effects on β-cell tone and responsiveness to glucose [21, 57, 120]. However, a recent demonstration that stimulation of α-cell secretion by gastric inhibitory polypeptide (GIP), a hormone released episodically after meals, promotes glucose tolerance through α-to-β-cell communication [70] suggests that proglucagon peptides are also a component of prandial insulin responses.

Effects of glucagon on energy intake and energy expenditure

The GCGR is expressed by neurons throughout the CNS, including regions in the brain that are central to metabolic regulation [121]. Glucagon moves into the brain from the circulation and administration of glucagon into the cerebroventricular system of rats suppresses food intake. It is unknown whether the discrete population of hindbrain neurons that are the sole source of proglucagon peptides in the brain [122] produce glucagon as well as GLP-1, or whether direct actions of glucagon on CNS neurons is part of physiological regulation. A stronger case can be made that glucagon suppresses appetite through activation of peripheral signals in the liver [121]. Stimulation of hepatic FGF-21 release by glucagon contributes to negative energy balance [123, 124]. This model has been developed in rodents, and is based on the relatively higher hepatic portal glucagon concentrations and a connection to the satiety centres of the hindbrain through vagal afferent fibres. While plausible, this remains hypothetical, with as yet no translation to humans.

While glucagon may reduce energy intake, it may also promote energy expenditure. In pre-clinical studies, glucagon increases both core body temperature [125] and brown adipose tissue mass and heat generation [125–128]. Brown adipose tissue is highly activated during cold exposure to maintain body temperature, and cold exposure increases both plasma glucagon levels and brown adipose tissue glucagon content in rats [129]. However, recent work in mice [130] and humans [131] has demonstrated that glucagon increases energy expenditure independently of brown adipose tissue activation. Moreover, while there are several studies showing that infusion of glucagon to humans for several hours causes a 10–20% increase in energy expenditure, this effect is not maintained over 24 hours [132]. Mice with deletion of the *Gcg* gene and an absence of proglucagon peptides were leaner than control mice, but did not differ in total body weight [133], suggesting that glucagon may have a minor role in determining adiposity. Thus, while there are both mechanistic and clinical data supporting glucagon action as a means to reduce energy balance, the magnitude of the effect does not appear to be large.

Production of glucagon-like peptide 1 by α cells

Glucagon is not the only important *Gcg* peptide with a role in intra-islet regulation, with recent studies suggesting that α-cell production of GLP-1 may also have a role in the regulation of islet function (Figure 8.4). Rodent islets studied in culture have demonstrable expression of PC1/3, and release fully processed, bioactive GLP-1 in culture [134, 135]. Moreover, intact GLP-1[7-36]-amide is secreted from isolated rat islets [134, 136], and from isolated human islets and α cells [137]. Interruption of GLP-1 receptor (GLP-1R) signalling in isolated rodent islets or pancreata, using receptor antagonists or gene knockout techniques, reduces basal [134] and glucose-stimulated insulin secretion [138]. These findings have recently been corroborated in a mouse model with β-cell–specific deletion of the GLP-1R [139]. Finally, infusion of a GLP-1R antagonist to fasting humans, with fixed, low circulating GLP-1 levels, decreases glucose-stimulated insulin secretion [140, 141]. These findings can be taken as support for the action of local islet GLP-1. Overall, there has been an accumulation of evidence to support a role for local production of GLP-1 in α-to-β-cell communication and the regulation of insulin secretion.

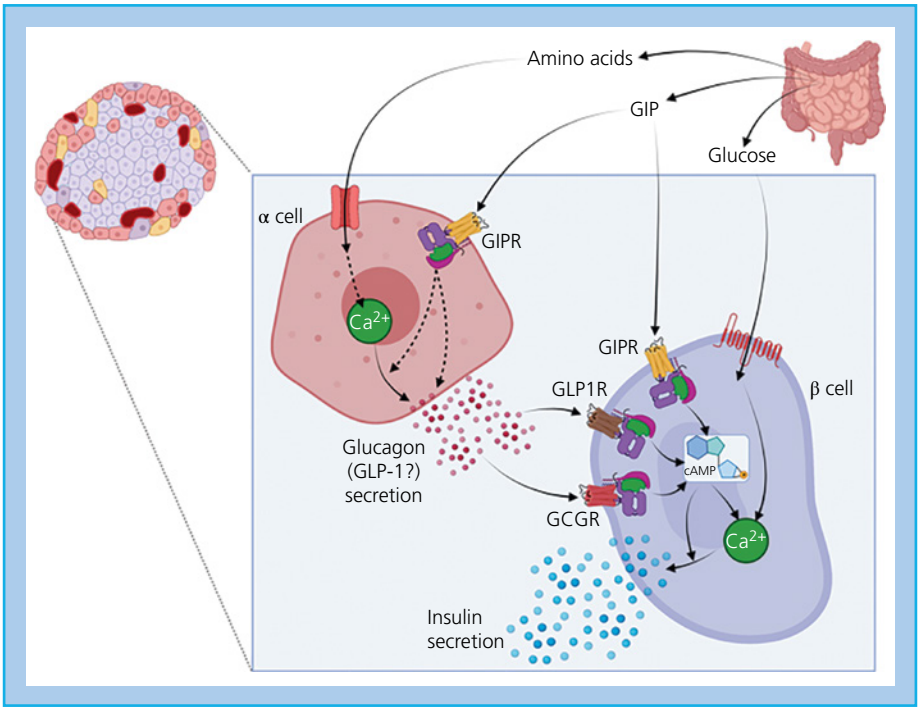

Figure 8.4 The integration of the incretin system and nutrient sensing in α and β cells in the post-prandial state. Feeding increases the plasma concentrations of glucose, amino acids, and glucose-dependent insulinotropic polypeptide (GIP). GIP potentiates glucose-stimulated insulin secretion in β cells and amino acid–stimulated glucagon secretion in α cells. The rise in glucagon, and potentially glucagon-like peptide 1 (GLP-1), secretion in α cells enhances α-to-β-cell communication, which is mediated by both the GLP-1 receptor (GLP-1R) and glucagon receptor (GCGR). The combined activation of GLP-1R, GCGR, and GIP in β cells produces maximal insulin secretion and glucose homeostasis.

Beyond a role in normal islet function, α-cell GLP-1 seems to be involved in response to stress and illness as well. In rats treated with the β-cell toxin streptozotocin, islet PC 1/3 and ProG expression, and processing of the pro-peptide to GLP-1, were increased [142]. Moreover, increased GLP-1 signalling in the islet was implicated in the recovery from injury. Islet GLP-1 production and action are also mediated by the cytokine interleukin (IL)-6, which is released in response to exercise, obesity, diabetes, and critical illness [143–145]. Expression of the IL-6 receptor is relatively high in α cells, and IL-6 signalling increases Gcg transcription and GLP-1 production in mice. Overall, the findings from these and other studies suggest that a paracrine system of islet GLP-1 signalling plays a role in several adaptations to metabolic stress. Understanding the control of the relative production of α-cell GLP-1 and glucagon would seem to hold promise for therapeutic development.

Abnormalities of glucagon secretion and action in diabetes

The potent effects of glucagon to promote fasting hepatic glucose production can be amplified in the setting of diabetes, where insulin secretion is impaired and insufficient for normal opposition of glucagon effects [146–148]. The secretion of both principal islet hormones, insulin and glucagon, is abnormal in people with diabetes. Plasma glucagon levels tend to be substantially elevated in suboptimally managed diabetes with severe insulin deficiency or ketoacidosis [9]. In a classic study using somatostatin to inhibit α-cell secretion, individuals with type 1 diabetes had substantial improvements in hyperglycaemia and ketogenesis when plasma glucagon was reduced [5]. Among groups with type 2 diabetes, some individuals will have modest fasting hyperglucagonaemia even without metabolic decompensation, and clinical studies suggest that this increase is sufficient to contribute to the elevated hepatic glucose production in individuals with diabetes [146, 149]. Moreover, in a group of individuals with type 2 diabetes who had suppression of islet hormone secretion by somatostatin, there was a significant reduction of basal hepatic glucose production, and this effect was enhanced when insulin was given at basal levels [9]. Together these findings exemplify the basis for concluding that glucagon action contributes to pathogenic elevations of fasting glucose in at least a subset of those with type 2 diabetes.

Similar to the β cell in individuals with diabetes, the α cell has abnormal sensitivity to glucose and is less suppressed during hyperglycaemia. As a result, plasma glucagon levels after mixed-nutrient meals are generally higher with type 2 diabetes [69, 150, 151]. In contrast, glucagon responses to hypoglycaemia are also reduced [69, 152]. The mechanism for this is not clear, but the functional result suggests another form of α-cell glucose insensitivity. There is emerging evidence that α-cell dysfunction in diabetes has a genetic origin. Specifically, a common polymorphism in the *KCNJ11* gene, which encodes the KIR6.2 component of the K_{ATP} channel, predisposes individuals to type 2 diabetes and is related to blunted glucose-induced suppression of glucagon [153, 154].

In addition to the effects of hyperglucagonaemia on fasting glucose levels, abnormal α-cell regulation also contributes to glucose intolerance. Following meals, glucagon levels remain abnormally elevated in individuals with diabetes, rather than undergoing the abrupt post-prandial decline typical of individuals without diabetes [155]. In normal physiological regulation, the post-prandial suppression of glucagon is a key factor in shifting hepatic metabolism from glucose production to glucose clearance [156], and failure to make this shift disrupts normal glycaemic regulation after meals. For example, individuals without diabetes have significantly greater glycaemic excursions after a test meal when glucagon levels are maintained at fasting concentrations compared to when they are allowed to follow the normal post-prandial decline [157]. Similar results can also be demonstrated in

individuals with type 2 diabetes [158]. Thus, failure to suppress fasting glucagon levels after a meal contributes to glucose intolerance, and this effect is magnified in the setting of diabetes where insulin secretion and action are reduced.

Pharmacology based on glucagon action

Exogenous glucagon has been used by individuals with diabetes for the acute treatment of hypoglycaemia for nearly 50 years. However, approaches to block glucagon action as a means of lowering blood glucose in individuals with diabetes go back nearly as far. Mouse models with interruption of glucagon receptor function [159, 160] or absence of α-cell secretion [161, 162] have lower fasting glucose and significantly improved glucose tolerance than control mice and provide proof of principle that long-lasting blockade of glucagon signalling could be an effective means of reducing diabetic hyperglycaemia. Despite these compelling findings, there is no approved drug that selectively blocks the effects of glucagon as a diabetes treatment. This is primarily due to findings in pre-clinical models and safety concerns with compounds tested in humans. Animal models with GCGR or Gcg deletion develop α-cell hyperplasia and/or profound elevations of circulating proglucagon-related peptides occur in mice with GCGR or Gcg deletion [163]; this has also been reported in humans with GCGR mutations [164]. In addition to the expansion of endocrine cells, animals deficient in glucagon signalling also have increased total pancreatic weight, reflecting expansion of the exocrine compartment. Moreover, lack of glucagon action is associated with reductions in hepatic lipid oxidation [165] and increased hepatic susceptibility to toxic injury [166]. Blockade of glucagon action in humans has been possible with several small-molecule GCGR antagonists. One of these compounds was demonstrated to block the actions of exogenous glucagon in individuals without diabetes [167], but was not further developed and no information on treatment of individuals with diabetes with fasting hyperglycaemia or endogenous hyperglucagonaemia was published. Other GCGR antagonists have been reported to lower fasting [168], and post-prandial [169], glucose in individuals with diabetes in a dose-responsive manner. As the pharmacological approach most analogous to genetic models of reduced GCGR signalling, antagonists have obvious potential as drugs to lower glucose and treat diabetes. However, the data from pre-clinical studies, and the failure of products tested in humans to progress from the trial stage, raise concerns that adverse effects such as α-cell hyperplasia, hepatic steatosis, or susceptibility to hepatic toxicity could occur in treated individuals (Figure 8.5). Moreover, the effects of these agents on glucose counter-regulation would need to be carefully assessed.

Importantly, there are now diabetes drugs available that work at least in part by inhibiting glucagon secretion. GLP-1 receptor agonists and DPP-4 inhibitors mimic the effect of endogenous GLP-1 to inhibit glucagon secretion and hepatic glucose production, and this contributes to their effect on improving glucose regulation in type 2 diabetes [170]. These compounds have achieved common usage in clinical practice. Administration of pharmacological amounts of GLP-1 to hyperglycaemic individuals with type 1 diabetes with minimal β-cell function reduced blood glucose by ~4 mmol/l, and this was associated with a 40–50% decrease in plasma glucagon [171].

A novel and exciting recent approach to treat type 2 diabetes has been the development of hybrid peptides that activate more than one receptor to generate an effect [172]. These agents are touted as

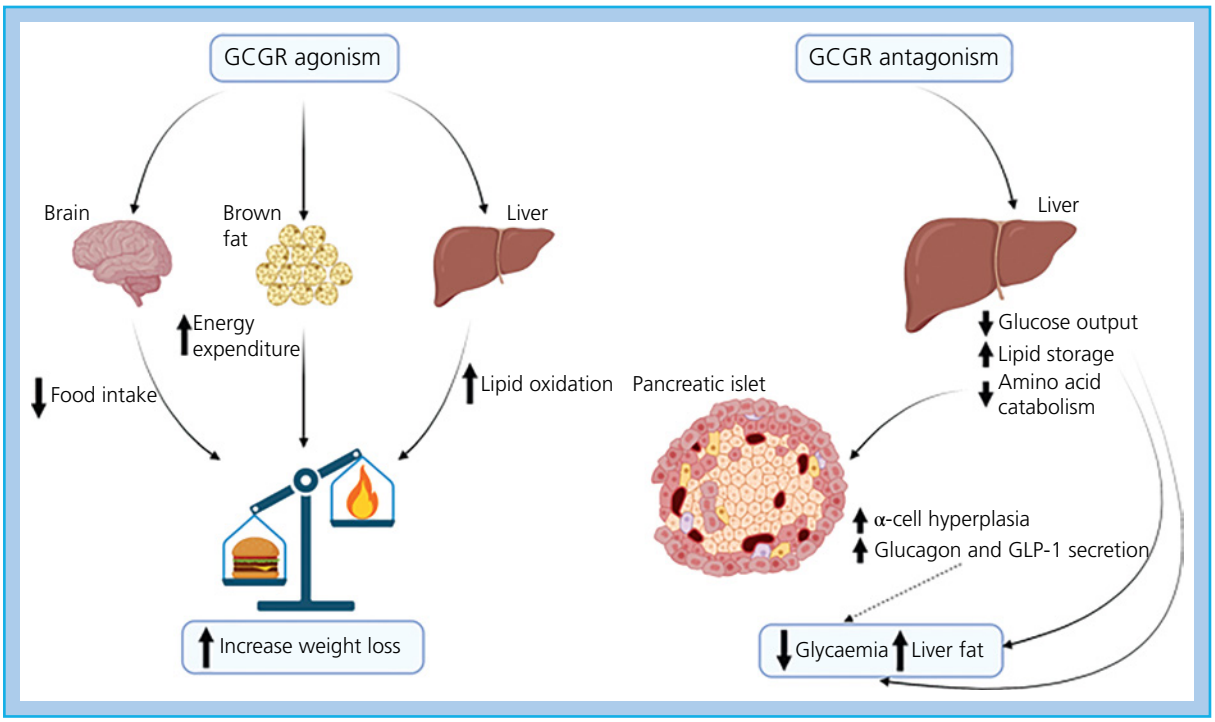

Figure 8.5 Glucagon receptor (GCGR) agonism vs antagonism. Glucagon receptor agonists enhance catabolic events including thermogenesis in brown adipose tissue and lipid oxidation in hepatocytes. This results in increase energy expenditure. Glucagon receptor agonism also reduces food intake. The overall effect is negative energy balance and potentially weight loss. Glucagon receptor antagonism reduces hepatic glucose output, lowering glycaemia. Glucagon receptor antagonism also prevents lipid oxidation and amino acid catabolism in hepatocytes. The rise in plasma amino acids provides a signal for α-cell hyperplasia, resulting in elevated concentrations of both glucagon and glucagon-like peptide 1 (GLP-1).

mimicking the broad range of hormonal changes associated with bariatric surgery, and the need to utilize more than one ligand-receptor system to achieve significant weight loss. Some of the first compounds developed using this strategy were targeted to the glucagon and GLP-1 receptors, peptides engineered to activate the cognate receptors of both peptides in different relative potencies [173, 174]. The rationale for this was that activating both glucagon and GLP-1, which bind to specific and distinct receptor populations in the brain to cause satiety [175, 176], might have synergistic results. Two different initial reports suggest that hybrid peptides with balanced GCGR and GLP-1R potency reduced body weight and fat, increased energy expenditure, and dramatically improved glucose tolerance in obese mice and rats [174, 177] (Figure 8.5). The effects on weight loss were significantly greater than that of a GLP-1R–only agonist, and this additive response supports differential activation of different neural pathways for glucagon and GLP-1 to cause weight loss. In humans, while GLP-1 infusion alone had no effect on energy expenditure, and glucagon infusion alone raised both blood glucose levels and energy expenditure, co-administration of both peptides increased energy expenditure but did not raise glucose levels [178]. The potential for a GLP-1R/GCGR co-agonist to raise blood glucose has also been demonstrated with oxyntomodulin [179], a Gcg product that activates both receptors. Thus, the coupling of GLP-1 activity has promise to provide greater weight loss effects than either compound administered alone, with hyperglycaemic actions of glucagon mitigated by GLP-1 signalling. Given the technology to engineer peptides with multireceptor effects and the dramatic responses in pre-clinical models, this is likely to be an area of active diabetes drug development in the future.

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9 Mechanism of Insulin Action

Morris F. White
Division of Endocrinology, Children's Hospital Boston, Harvard Medical School, Boston, MA, USA

Key points

- The insulin receptor is a transmembrane protein. The α subunits of the insulin receptor are entirely extracellular and create the ligand binding sites. The β subunits contain a transmembrane-spanning segment that separates the extracellular regions from the intracellular tyrosine kinase.
- Insulin and insulin-like growth factor (IGF) signalling integrates the storage and release of nutrients with animal growth during development and tissue maintenance throughout life.
- The human genome encodes a superfamily of structurally related insulin-like peptides including insulin, insulin-like growth factor-I (IGF-I), and insulin-like growth factor-II (IGF-II), which activate five receptor tyrosine kinases assembled from two genes.
- Insulin resistance, the reduced responsiveness of tissues to normal insulin concentrations, is an important risk factor for the metabolic syndrome and its progression to cardiovascular disease, non-alcoholic fatty liver disease, and type 2 diabetes.
- Insulin receptor substrate (IRS) proteins are composed of tandem structurally similar pleckstrin homology and phosphotyrosine binding domains followed by a long, unstructured tail of tyrosine and serine phosphorylation sites that coordinate insulin and IGF signalling. These domains are strongly conserved in IRS from *Drosophila* (Chico), zebra fish, mouse, chimpanzee, and human.
- During insulin and IGF-I stimulation, some tyrosine residues in the IRS tail are phosphorylated and bind to the Src homology 2 (SH2) domains of various signalling proteins, including the 85 kDa regulatory subunit (p85) of the PI3K and the RAS GTP exchange factor Grb2·Sos.
- IRS1 expression can be regulated by transcriptional repressors, including transcription factor AP-2-beta (AP2β) or the p160 family of nuclear receptor coactivators p/CIP (p300/CBP/cointegrator-associated protein) and SRC1 (steroid receptor coactivator-1).
- IRS2 transcription is regulated by multiple factors, including cyclic adenosine monophosphate (cAMP) response element binding protein (CREB) and its coactivator CREB-regulated transcription coactivator 2 (CRTC2), FOXO1/3, nuclear factor of activated T cells (NFAT), transcription factor E3 (TFE3), hypoxia-inducible factor-2α encoded by Epas1 (HIF2α), and sterol regulatory element binding protein 1 (SREBP1).
- IRS1 and IRS2 can be polyubiquitinylated during chronic inflammatory states, nutrient excess, and hyperinsulinaemia through various tissue-specific mechanisms.
- Several pathways are known to promote degradation of IRS1 or IRS2: (i) proinflammatory cytokine-mediated upregulation of SOCS1/3 (suppressors of cytokine signalling); (ii) the cullin-RING E3 ubiquitin ligase 7 (CRL7); (iii) Cbl proto-oncogene B (CBLB), a RING-type E3 ubiquitin ligase; and (iv) mitsugumin 53 (MG53), a tripartite motif-containing (TRIM) family E3 ubiquitin ligase.
- IRS1 and IRS2 can be regulated through a complex mechanism involving phosphorylation of more than 50 serine/threonine residues located in the long-tail regions.
- Pancreatic β cells have a special place in nutrient homeostasis as the unique source of insulin secretion, and like other cells they also require insulin and IGF signalling for growth, function, and survival. Since β cells are always exposed to insulin and IGF, the signalling appears to be regulated through multifactor transcriptional control.

Insulin and insulin-like growth factor (IGF) signalling integrates metabolism, growth, reproduction, and lifespan with environmental signals [1]. Lower animals express many insulin-like peptides – 38 in *Caenorhabditis elegans* and 7 in fruit flies – that bind to a single insulin-like receptor tyrosine kinase [2], whereas the human genome encodes a smaller family of structurally related insulin-like peptides, including insulin itself, IGF-I, and IGF-II. Diabetes is a common metabolic disease of persistent hyperglycaemia owing to various mechanisms that cause deficiency of insulin and/or insulin action, including impaired glucose sensing or insulin secretion by pancreatic β cells (maturity-onset diabetes of youth, MODY); autoimmune-mediated β-cell destruction (type 1 diabetes); or insufficient β-cell insulin secretory capacity to compensate for peripheral insulin resistance (type 2 diabetes) [3]. MODY is caused by mutations in at least 14 genes associated with β-cell function, notably hepatocyte nuclear factor-4α (*HNF4α*, *MODY1*), glucokinase (*GCK*, *MODY2*), and hepatocyte nuclear factor-1α (*HNF1α*, *MODY3*) [4].

During the past 50 years, advances in all areas of biomedical science led to a multidisciplinary understanding of insulin receptor signalling. Cloning of the insulin receptor cDNA and its gene revealed novel mechanisms of signal transduction. Dysregulated insulin signalling causes insulin resistance, which includes any state of diminished cellular or systemic insulin action [5]. Mutations in

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the insulin receptor were thought to be plausible genetic candidates for insulin resistance [6]; however, after considerable investigation insulin receptor mutations were only identified in very rare cases of severe insulin resistance, but not associated with type 2 diabetes [7]. Physiological, immunological, and metabolic stresses are common causes of chronic insulin resistance, which can lead to type 2 diabetes when pancreatic β cells fail to secrete sufficient insulin to promote an adequate insulin response [8]. Variations in over 100 genetic loci, including variations in MODY genes, are associated with some of the heritability of type 2 diabetes (Chapter 12) [9, 10]. Regardless, which genetic variations might reveal a short list of new *drugable* targets to prevent type 2 diabetes continues to be a challenging clinical and scientific problem [11, 12].

Insulin

Insulin is synthesized in pancreatic β cells as a single polypeptide called proinsulin that is processed by prohormone convertase-1/3 (PCSK1) to excise the C-peptide and generate the bioactive disulfide linked A-chain and B-chain. Insulin is composed of three α-helices – one in the B-chain and two in the A-chain [1]. Insulin dimerizes through a β-sheet between the C-terminus of the B-chains, including residues Phe^{B24}, Phe^{B25}, Tyr^{B26}, Thr^{B27}, Pro^{B28}, Lys^{B29}, Thr^{B30}, Phe^{B24}, Phe^{B25}, and Tyr^{B26} [13]. Three insulin dimers form a hexamer in the presence of zinc [14]. Biochemical and genetic analysis reveals two asymmetrical receptor binding surfaces called the primary or classical site (S1) and the second or novel site (S2) (Figure 9.1) [15]. Natural mutations, alanine scanning mutagenesis, and structural refinements show that S1 includes residues from the A- and B-chains of insulin, including Val^{B12}, Tyr^{B16}, Gly^{B23}, Phe^{B24}, Phe^{B25}, Tyr^{B26}, Gly^{A1}, Gln^{A5}, Tyr^{A19}, and Asn^{A21} (Figure 9.1a) [16, 17]. The Phe^{B24}–Phe^{B25}–Tyr^{B26} motif at the end of the B-chain undergoes a conformational change to expose the S1 for high-affinity binding (K_d ~0.25 nmol/l) (Figure 9.1b) [1, 13, 18]. At high concentrations, a second or novel site was discovered on the opposite side of insulin that is composed of different A- and B-chain residues, including His^{B10}, Glu^{B13}, Leu^{B17}, Ser^{A12}, Leu^{A13}, and Glu^{A17} (Figure 9.1a) [14, 15, 19]. The second site binds with lower affinity to a different location on the insulin receptor [13].

Insulin receptor

Extracellular domain of the insulin receptor

The insulin receptor proreceptor is a 150 kb gene comprising 22 exons on human chromosome 19p13.3–p13.2 that encodes the extracellular and intracellular domains (Figure 9.2a). During synthesis, the proreceptor enters the endoplasmic reticulum where it is glycosylated and stabilized by disulfide bonds. Next it migrates into the Golgi, where furin cleaves at the Arg-Lys-Arg-Arg motif to generate the αβαβ-dimer (Figure 9.2a) [14, 20]. The extracellular domain comprises the α-subunit and an NH_2-terminal portion of the β-subunit. The α-subunit begins with two NH_2-terminal leucine-rich repeats (L1, aa1–155; and L2, aa315–470) flanking a cysteine-rich (CR, aa195–310) region containing eight modular cysteine-linked repeats (Figure 9.2a). These modules are followed by three fibronectin-III motifs, including $Fn_{iii}1$ (aa473–591) and $Fn_{iii}3$ (aa808–904) flanking $Fn_{iii}2$ (aa597–717), which are interrupted by a 120 amino acid insert domain containing the furin cleavage site (IDa, aa636–690) (Figure 9.2a).

The disulfide-linked α-subunits and extracellular portion of the β-subunits fold into an inverted V configuration with the apex formed by L2 and $Fn_{iii}1$ domains (Figure 9.2b) [13]. Natural and site-directed mutagenesis, photo-affinity labelling, and structural refinements predicted the location of two insulin binding sites in the α-subunit. The high-affinity S1 is composed of the L1 domain from one α-subunit and CTα′ (aa 693–710) from the other (Figure 9.2c) [13, 19, 21]. When the insulin receptor is saturated by high insulin concentrations, cryo-EM reveals the location of a distinct low-affinity S2 near the $Fn_{iii}1 \rightarrow Fn_{iii}2a$

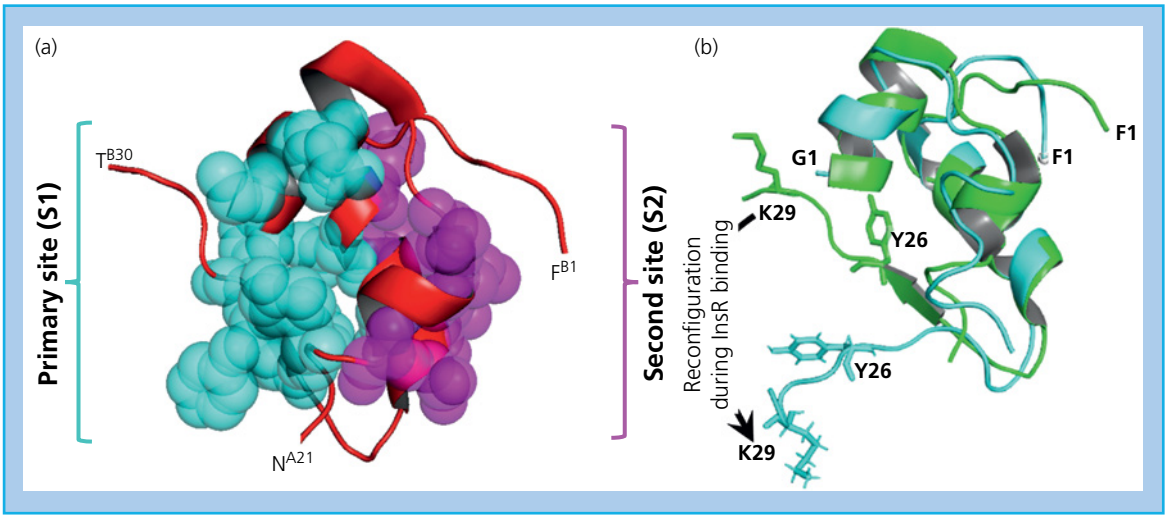

Figure 9.1 (a) Pig insulin structure (pdb id: 4ins) showing the position of some critical amino acids that compose the two binding surfaces (S1 and S2) that interact with the L1•CR•CT and $Fn_{iii}1$•$Fn_{iii}2$ domains of the insulin receptor, respectively. The primary receptor bind site (S1) is shown in cyan, and the secondary site (S2) is shown in violet as space-filling residues. The amino terminal residue of the B-chain and the carboxy terminal residue of the A- and B-chains are labelled. (b) Structural alignment of free insulin (green) and insulin (pdb id: 6sof) bound to the high-affinity site on the insulin receptor (cyan). Cartoons are created in PyMOL Molecular Graphics System, Version 2.0, Schrödinger, LLC.

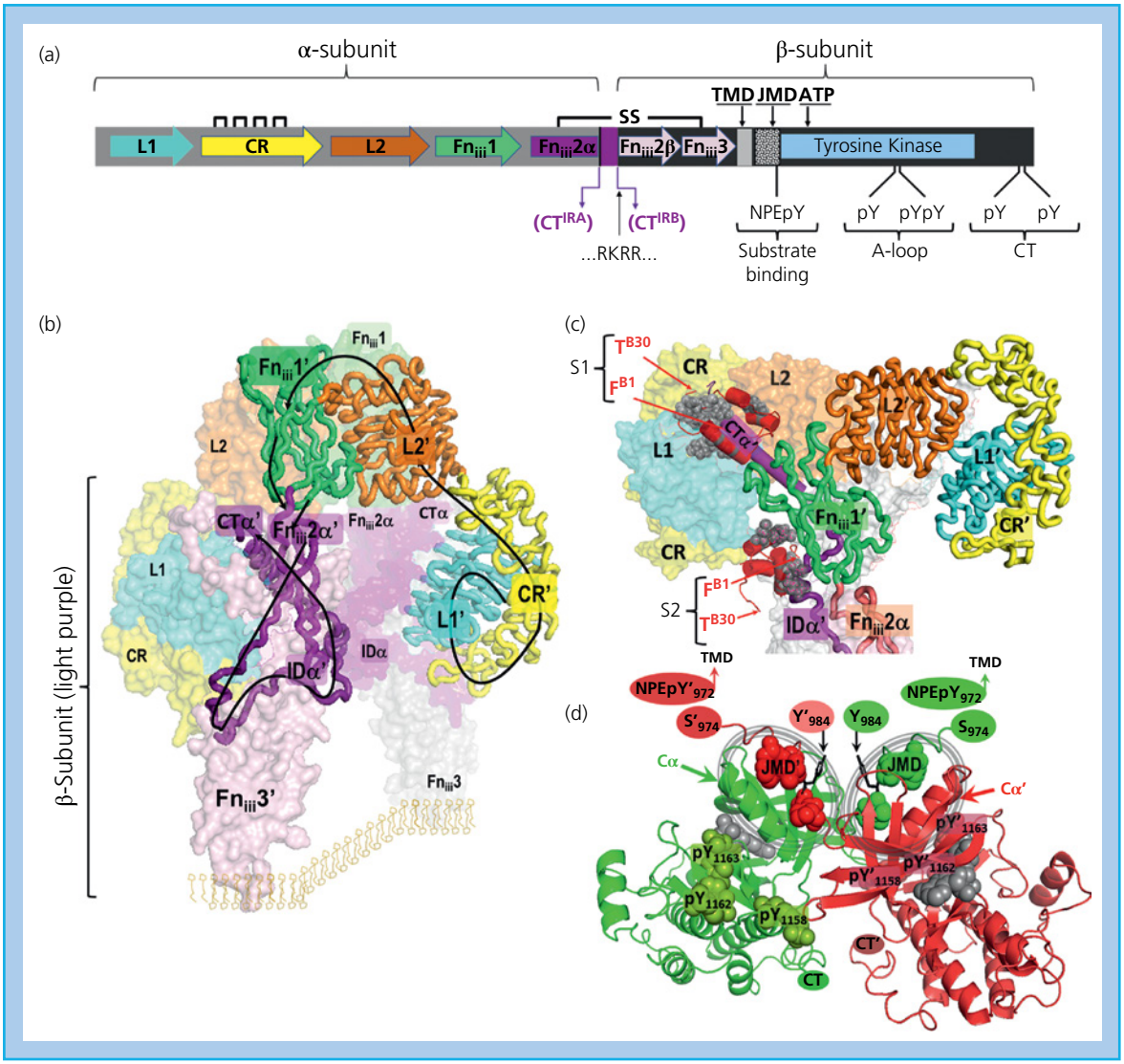

Figure 9.2 (a) Diagram of the insulin receptor precursor showing the position of important domains, including two leucine-rich regions (L1 and L2) flanking a cysteine-rich region (CR); fibronectin iii domains ($Fn_{iii}1$, $Fn_{iii}2a$, $Fn_{iii}2b$, $Fn_{iii}3$); the insert domains IDa and IDb flanking the Arg-Lys-Arg-Arg furin cleavage site; the alternative IRA/IRB splice site that generates the short CT^{IRA} or long CT^{IRB}; a transmembrane domain (TMD); the IRS binding motif (NPEpY); the A-loop (activation loop) autophosphorylation sites; and carboxyl terminal tyrosine phosphorylation sites (CT). (b) Cartoon of the inactive conformation of the ectodomain of the insulin receptor (pdb id: 6pxv). The insulin receptor subunit is shown as a ribbon diagram with the labelled structural domains, L1′, CR′, L2′, $Fn_{iii}1'$, $Fn_{iii}2a'$, and CTa′ traced with a black line; $Fn_{iii}2b'$ and $Fn_{iii}3'$ are shown in light purple and grey space-filling structures, respectively. The other insulin receptor subunit is shown as a space-filling structure in the background: L1 (cyan), CR (yellow), L2 (orange), $Fn_{iii}1$ (green), $Fn_{iii}2a$ (purple), and CTa (purple). $Fn_{iii}2b'$ and $Fn_{iii}3'$ are shown in light pink. (c) The structure of the ectodomain of the insulin receptor in the T conformation with insulin bound at S1 and S2. Note the different orientation of each insulin molecule revealed by the position of the B-chain residues F^{B1} and T^{B30}. (d) The dimeric structure of the juxtamembrane domain (JMD) of the insulin receptor shown in green (IRK) and red (IRK′). The grey oval highlights the dimerization region between the juxtamembrane domain and the Ca/b-sheet. Phosphorylated residues of the A′-loop are shown in red (insulin) and green (insulin receptor).

interface (Figure 9.2c) [22–25]. Insulin binding to S1 crosslinks the α-subunits to stabilize the extracellular domain in a T conformation, which might cause the $Fn_{iii}3 \rightarrow$ transmembrane domain (TMD) to converge and facilitate transphosphorylation of the intracellular receptor tyrosine kinase (Figure 9.2d) [13, 26, 27].

Exon-11 of the insulin receptor gene is alternatively spliced depending on the tissue and developmental stage to produce two insulin receptor isoforms, including IRA that omits exon-11 and IRB that includes exon-11 to add 12 amino acids at the C-terminus of the α-subunit (CTα) [15]. Insulin binds with high affinity to the homodimeric IRB ($\alpha\beta^{IR}\bullet\alpha\beta^{IR}$), which predominates in adult liver, muscle, and adipose tissues. IRA binds insulin with slightly lower affinity, but unlike IRB also binds IGF-I and IGF-II in the physiological range [28, 29].

Receptor tyrosine kinase

Most receptor tyrosine kinases reside in the plasma membrane as monomers that form homo- or heterodimers on ligand binding to promote transphosphorylation and signal transduction. Since the insulin receptor is a covalent dimer, a different mechanism inhibits transphosphorylation of the cytoplasmic receptor tyrosine kinase until insulin binds. The intracellular portion of the insulin receptor

β-subunit begins with a 30-residue juxtamembrane domain between the TMD and the receptor tyrosine kinase that terminates with the 70-residue carboxy-terminus (Figure 9.2a) [26]. Each intracellular region contains tyrosyl phosphorylation sites (numbered as in IRB): Y_{965} and Y_{972} in the juxtamembrane domain; Y_{1158}, Y_{1162}, and Y_{1163} in the activation loop (A-loop) of the kinase domain; and Y_{1328} and Y_{1334} in the carboxy-terminus [30–32]. Recent analysis using liquid chromatography–tandem mass spectrometry revealed several serine phosphorylation sites, including S_{968}, S_{969}, S_{974}, and S_{976} in the juxtamembrane domain; and S_{1278}, S_{1320}, S_{1321}, and T_{1348} in the carboxy-terminus [32].

Before insulin binds, the catalytic activity of the insulin receptor is inhibited by interactions between Tyr_{984} in the juxtamembrane domain with a hydrophobic pocket created from an α-helix (αC) and a five-stranded β-sheet in the N-terminal lobe of the receptor tyrosine kinase. This interaction inhibits transphosphorylation of the adjacent receptor tyrosine kinases by preventing the α-helix from assuming its catalytically active position [26,33,34]. Both receptor tyrosine kinase domains are inhibited until the ectodomains converge during insulin binding, which is thought to facilitate transphosphorylation in the A-loop (Figure 9.2c) [35]. Multisite transphosphorylation in the A-loop releases several inhibitory mechanisms [30]:

- The unphosphorylated Tyr_{1162}, the second of the three A-loop tyrosine residues, blocks access of peptide substrates to the active site.
- Asp_{1161} preceding Tyr_{1162} stabilizes the closed A-loop to inhibit unstimulated transphosphorylation [36].
- The NH_2-terminal end of the A-loop (D_{1150}FG-motif) competes to elevate the K_m for adenosine triphosphate (ATP) [37].

Intramolecular transphosphorylation begins at Tyr_{1158} and progresses to Tyr_{1162} and slowly to Tyr_{1163} until tris-phosphorylation stabilizes the open A-loop to fully activate the kinase [38,39]. This model is confirmed by an $Asp_{1161} \rightarrow$ Ala substitution that shifts the A-loop towards the open configuration, increasing basal activity [36]. Substitution of Tyr_{1162} with phenylalanine also increases basal transphosphorylation consistent with its role to stabilize the closed conformation or block ATP and protein substrate entry into the active site [40,41]. Transphosphorylation appears to destabilize the cis-interaction between Tyr_{984} and α-helix [26], creating a new trans-interaction between Tyr_{984} and αC′ or Tyr_{984}′ and the α-helix of adjacent receptor tyrosine kinases (Figure 9.2d). Thus, kinase activation involves both activation-loop phosphorylation and conformation rearrangements that stabilize the receptor tyrosine kinase dimer, so that the catalytic sites are exposed on opposite sides of the insulin receptor kinase to phosphorylate IRS-proteins or SHC recruited by the NPEpY-motif (Figure 9.2d).

Insulin signalling cascade

Following discovery of the insulin receptor tyrosine kinase, many groups searched for cellular proteins that might mediate downstream signals [42,43]. The first evidence for a substrate of any receptor tyrosine kinase came from anti-phosphotyrosine antibody immunoprecipitates that revealed a 185-kDa phosphoprotein (pp185) in insulin-stimulated hepatoma cells [44]. Purification and molecular cloning of pp185 revealed the first member of a family of signalling scaffolds engaged by receptor tyrosine kinases and the first insulin receptor substrate called IRS1 [45]. Three homologous IRS-protein genes are expressed in human tissues, including IRS1, IRS2, and IRS4; rodents also express IRS3 in adipose tissue [46]. IRS1 and IRS2 are broadly expressed in mammalian tissues, whereas IRS4 is mainly restricted to the hypothalamus and some cancer tissues [47–52] (Figure 9.3). Work with transgenic mice reveals that systemic insulin signalling is largely mediated through IRS1, IRS2, or both.

IRS proteins couple the insulin receptor to the downstream signalling cascade

IRS proteins are composed of tandem structurally similar pleckstrin homology (PH) and phosphotyrosine binding domains followed by an unstructured tail of tyrosine phosphorylation sites that coordinate downstream signals (Figure 9.4). IRS proteins also contain serine/threonine phosphorylation sites, which modulate insulin signalling through feedback or heterologous mechanisms. IRS proteins are strongly conserved from *Drosophila* (Chico) to humans. On insulin stimulation, the IRS proteins are recruited to the juxtamembrane domain of the activated insulin receptor kinase, where several tyrosine residues in the unstructured tail are phosphorylated. These phosphorylated residues bind to the Src homology 2 (SH2) domains in various signalling proteins, especially the 85 kDa regulatory subunits (p85) of the phosphatidylinositol 3-kinase (PI3K) (Figure 9.4). The binding between phosphorylated YMPM-motifs in IRS1 and both SH2 domains in PI3K was the first insulin signalling cascade to be reconstituted *in vivo* and *in vitro* (Figure 9.4) [53]. Tyrosine phosphorylation of other sites in IRS1 or SHC adaptor protein 1 (SHC) can recruit Grb2•SOS, which activates the mitogen-activated protein kinase (MAPK) cascade composed of RAS → MEK → ERK (Figure 9.4).

Tyrosine phosphorylation of specific residues in IRS is accomplished through at least two mechanisms:

- Specific recruitment of the phosphotyrosine binding domain of IRS or SHC to the phosphorylated NPEpY motif in the juxtamembrane domain of the insulin receptor.
- Recognition of specific phosphorylation motifs in the tail by the activated insulin receptor catalytic domain.

The $NPEpY_{972}$ motif in the juxtamembrane domain fills an L-shaped cleft on the phosphotyrosine binding domain [54,55]; however, the $NPEpY_{972}$ motif has low affinity for the phosphotyrosine binding domain of IRS1 (Kd ~87 mM), owing to a destabilizing effect of E_{971} that is essential for autophosphorylation of Y_{972} [37,56]. By comparison, the phosphotyrosine binding domain of SHC binds to $NPEpY_{972}$ with a much higher affinity (K_d ~4 mM) (Figure 9.4). Regardless, the structurally similar but functionally distinct PH domain immediately upstream of the phosphotyrosine binding domain helps recruit IRS to the insulin receptor (Figure 9.4) [57–59]. This interaction appears to be specific, as heterologous PH domains borrowed from other proteins reduce insulin receptor signalling [58,60]. The PH domains of some proteins bind inositol phospholipids to mediate membrane localization and signalling; however, the large majority of PH domains do not bind strongly to phosphoinositides and presumably mediate other functions [61]. The PH domain in the IRS proteins can bind acidic peptide motifs [60]. Whether the PH domain interacts with pSer residues in the juxtamembrane domain or C-terminal of the insulin receptor has not been tested, and whether the PH domain binds pSer residues in IRS itself is worth investigating [32].

IRS2 utilizes an additional mechanism, the kinase regulatory-loop binding (KRLB) domain, to interact with the insulin receptor (Figure 9.3) [62,63]. Structure analysis reveals that Tyr_{621} of

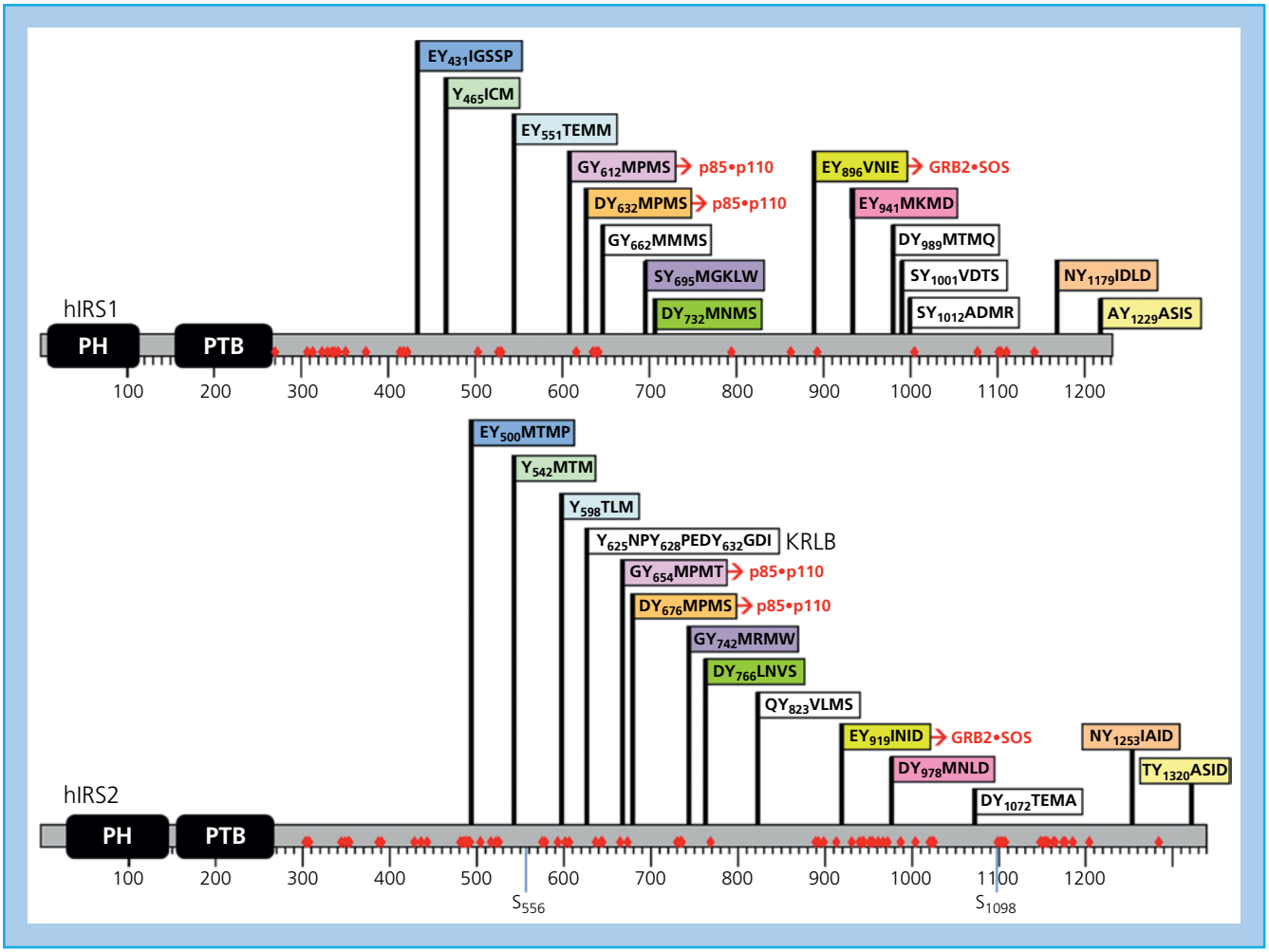

Figure 9.3 Alignment of IRS1 and IRS2 tyrosine phosphorylation sites relative to the amino-terminal pleckstrin homology (PH) and phosphotyrosine binding domains. Conserved tyrosine phosphorylation motifs including their number in the human protein and the surrounding amino acid sequences are colour coded to highlight alignments; white boxes indicate unique sites in IRS1 or IRS2. The relative positions of Ser/Thr-phosphorylation sites in IRS1 or IRS2 revealed by tandem mass spectrometry are indicated with red diamonds (♦). The unique kinase regulatory loop binding (KRLB) domain is indicated in IRS2 but not conserved in IRS1.

IRS2 inserts into the receptor ATP binding pocket, while Tyr_{628} aligns for transphosphorylation [64]. This interaction might promote IR → IRS2 signalling, since the KRLB interaction is apparently absent in the type 1 IGF receptor [64].

Phosphatidylinositol 3-kinase → AKT cascade

Phosphatidylinositol 3-kinase

The PI3K → AKT cascade begins when insulin stimulates tyrosyl phosphorylation of YMPM motifs in IRS proteins, which directly bind and activate the class 1A phosphotidylinositide 3-kinase (PI3K) (Figure 9.4) [65]. PI3K comprises a catalytic and a regulatory subunit. The catalytic subunit, including the widely expressed p110α (PIK3CA) and p110β (PIK3CB), and the leucocyte-restricted p110δ (PIK3CD) and p110γ (PIK3CG), is inhibited and stabilized on association with an 85 kDa regulatory subunit. Several regulatory subunits exist, including p85α (PIK3R1) and p85β (PIK3R2), alternative splicing of PIK3R1 to produce p55α or p50α, and PIK3R3 that encodes p55γ. The short homologues lack some NH_2-terminal regulatory features of p85 while retaining affinity towards the catalytic subunits [66,67]. All the regulatory subunits contain two SH2 domains that bind phosphorylated YXXM motifs, which disinhibit the catalytic domain to produce phosphatidylinositol 3,4,5-trisphosphate (PI(3,4,5)P3) [68–70]. Deletion of p85a or p85b also increases PI3K activity, which promotes insulin sensitivity [71,72]. By contrast, inhibition of the PI3K catalytic activity by chemical or genetic means blocks almost all metabolic responses stimulated by insulin, including glucose influx, glycogen and lipid synthesis, and adipocyte differentiation, confirming that PI3K is a critical node coordinating insulin action [73]; however, p110α inactivation might benefit metabolism during ageing owing to less downregulation of IRS protein levels [74].

On binding of p85 to phosphorylated YMPM motifs in IRS, the activated PI3K converts PI(3,4)P2 into PI(3,4,5)P3 that binds to the PH domains in specific signalling proteins to recruit and activate them at the plasma membrane, including 3′-phosphoinosotide-dependent protein kinase-1 (PDK1), v-akt murine thymoma viral oncogene (AKT), and target of rapamycin complex 2 subunit MAPKAP1 (SIN1). AKT is activated by phosphorylation at Thr_{308} in the A-loop ($pT308^{AKT}$) by the juxtaposed PDK1 (Figure 9.4). SIN1 is recruited to the plasma membrane by PI(3,4,5)P3, where it is phosphorylated at Thr_{86} by $pT308^{AKT}$. SIN1

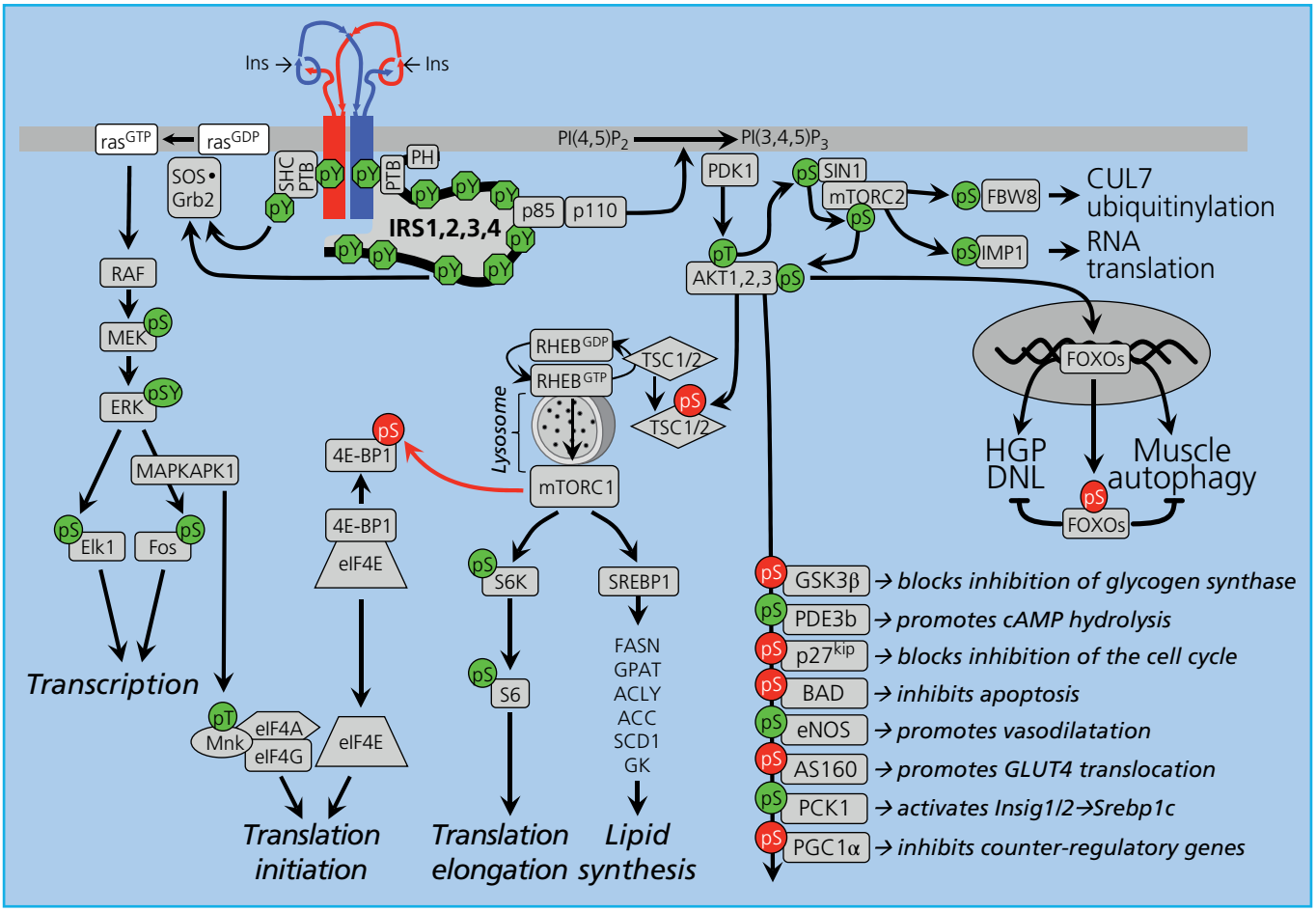

Figure 9.4 A canonical insulin signalling cascade. Two main branches mediate insulin signals initiated by tyrosine phosphorylation of the IRS proteins that bind and activate the phosphatidylinositol 3-kinase (PI3K) (p85•p110) and GRB2•SOS cascades. The Grb2/SOS complex promotes GDP/GTP exchange on $p21^{ras}$, which activates the ras → raf → MEK → ERK1/2 cascade. Activated ERK stimulates transcriptional activity by direct phosphorylation of ETS domain-containing protein (ELK1) and by indirect phosphorylation of cFOS through MAPK-activated protein kinase-1 (MAPK-APK1). The activation of PI3K by recruitment to IRS produces $PI3,4P_2$ and $PI3,4,5P_3$ (antagonized by the action of PTEN or SHIP2), which recruits PDK1 and AKT to the plasma membrane. AKT is activated in two steps. First, AKT is phosphorylated at T308 by PDK1. $T308^{AKT}$ phosphorylates SIN1 to activate mTORC2, which then phosphorylates $S473^{AKT}$. mTORC1 is activated by $Rheb^{GTP}$, which accumulates on inhibition of the GAP activity of the TSC1•TSC2 complex following AKT-mediated phosphorylation of TSC2. mTORC1 mediates phosphorylation of S6K and SREBP1, which promotes protein or lipid synthesis, respectively. AKT phosphorylates many cellular proteins inactivating PGC1α, $p21^{kip}$, GSK3α, BAD, and AS160, and activating PDE3β, PCK1, and eNOS. AKT-mediated phosphorylation of FOXO1 causes their sequestration and degradation in the cytoplasm, which inhibits their influence on transcriptional activity. Insulin stimulates protein synthesis by altering the intrinsic activity or binding properties of key translation initiation and elongation factors (eIFs and eEFs, respectively) as well as critical ribosomal proteins.

complexes with mTORC2, which phosphorylates $S473^{AKT}$ [75]. Bis-phosphorylated AKT can phosphorylate a wide array of substrates, including FOXO transcription factors (Figure 9.4). In adipocytes and muscle, SIN1 can recruit atypical protein kinase C (aPKC) to PI(3,4,5)P3, where it can be activated by PDK1 and promote insulin-stimulated glucose uptake [67,76,77]. Finally, SIN1 can be phosphorylated by ribosomal protein S6 kinase B1 (S6K1), which creates a feedback mechanism to inhibit mTORC2 [75,78,79].

AKT

Mammalian AKT1, -2, and -3 phosphorylate more than 100 substrates that control cell survival, growth, proliferation, angiogenesis, metabolism, and migration (Figure 9.4). Although overlap exists, AKT1 mainly regulates development, growth, and survival, whereas AKT2 regulates metabolism through insulin-stimulated glucose-transporter type 4 (GLUT4) translocation and liver glucose and lipid metabolism [80]. Humans with a rare dominant negative mutation in AKT2 display features of type 2 diabetes [81]. AKT3 promotes neuronal development, and homologous glucocorticoid-regulated kinase 3 (SGK3) synergizes with AKT2 in pancreatic β cells to stimulate proliferation and insulin release [82,83].

mTORC1

mTOR (mechanistic target of rapamycin) is a Ser/Thr kinase that belongs to the PI3K-related kinase family and forms two large functionally distinct protein complexes, mTORC1 and mTORC2, owing to the assembly of common and unique subunits [84]. Both complexes are controlled by insulin and other growth factors through the PI3K → AKT cascade; however, each complex is recruited to different compartments and respond distinctly to nutrients, stress, hypoxia/energy status, and other regulators [84]. mTORC1 is targeted to the lysosome where it is inhibited by the TSC1•TSC2 complex until AKT phosphorylates and inhibits tuberin (TSC2), a GTPase-activating protein (GAP), promoting GTP•RHEB (Ras homolog enriched in brain)

accumulation (Figure 9.4). FK506 binding protein 8 (FKBP38) inhibits mTORC1 until RHEB•GTP promotes its dissociation from mTORC1 [85]. Regulation by TSC1•TSC2 → RHEB is also modulated by AKT-mediated phosphorylation of AKT1S1 (AKT substrate 1, PRAS40), which promotes its dissociation from RAPTOR to activate mTORC1 [82]. RHEB resides on endomembranes including lysosomes where it can interact with mTORC1 only if enough amino acids are available to ensure that the cellular environment is sufficient to support growth (Figure 9.4) [86, 87]. Activated mTORC1 promotes many cellular anabolic processes needed for growth and proliferation, including the stimulation of glycolytic flux and mitochondrial function, protein and lipid synthesis, and the inhibition of autophagy and lysosomal biogenesis [79]. mTORC1 promotes the trafficking, processing, and transcription of sterol regulatory element binding proteins (SREBPs), which promotes transcriptional activity that stimulates lipogenesis (Figure 9.4) [88]. Thus, the IRS → PI3K → AKT → mTORC1 cascade controls many key cellular processes that balance cellular integrity, long-term growth, and survival.

mTORC2

In addition to fully activating AKT, mTORC2 plays a role in mRNA processing when it phosphorylates IGF-II mRNA-binding protein 1 (IMP1), which promotes IGF-II-leader 3′-mRNA translational initiation by internal ribosomal entry (Figure 9.4) [89]. Thus, mTORC2 can promote growth by regulating IGF-II production that can activate IRA in the mouse embryo. mTORC2 also regulates protein ubiquitinylation by phosphorylating F-box and WD repeat domain containing 8 (FBW8), a Cullin 7 E3 ubiquitin ligase recognition subunit (Figure 9.4). The phosphorylation of FBW8 stabilizes and promotes ubiquitinylation of targeted substrates, including IRS1 that contributes to insulin resistance in certain tissues and cells (Figure 9.4) [90]. Thus, mTORC2 signalling can modulate insulin signalling through its direct effect on AKT activity and various feedback regulatory nodes [89].

FOXO

Forkhead box O subfamily (FoxOs) – FOXO1, FOXO3a, FOXO4, and FOXO6 – are integrative transcription factors that control target gene expression to coordinate many biological processes including metabolism, autophagy, apoptosis, ROS detoxification, DNA repair, cell cycle, stem cell maintenance, and longevity [91]. FOXOs contain five highly conserved domains, including the N-terminal region with several AKT phosphorylation sites [92]; a highly conserved forkhead DNA binding domain; a nuclear localization signal located just downstream of the DNA binding domain; a nuclear export sequence; and a C-terminal transactivation domain [93]. Retention of FOXO in the nucleus promotes or suppresses gene expression by binding to TTGTTTAC motifs [94]. FOXO nuclear localization is regulated by various post-translational modifications including acetylation, methylation, glycosylation, ubiquitylation, and phosphorylation [95]. FOXO phosphorylation by AKT or other kinases including IκB kinase (IKK) and SGK promotes nuclear exclusion [92, 94]. Deacetylation of FOXOs by Silent mating type information regulation NAD-dependent deacetylase (SirT1) can suppress transcriptional activity directly [96].

FOXOs regulate metabolism by inducing genes that promote hepatic glucose production; insulin secretion in β cells and β-cell growth and differentiation; and fat and muscle mass [97–99]. In mammalian liver, decreased circulating insulin during fasting promotes the nuclear localization of FOXO, where it interacts with Ppargc1α, peroxisome proliferator-activated receptor gamma coactivator 1α (PGC1α), and cAMP response element-binding protein complexed with CREB regulated transcription coactivator 2 (CREB•CRTC2) to increase the expression of glucose-6-phosphatase (G6PC) and phosphoenolpyruvate carboxykinase 1 (PCK1) for hepatic glucose production [100]. FOXO also regulates hundreds of other hepatic genes directly or indirectly to coordinate glucose and lipid homeostasis and systemic insulin sensitivity. During fasting or insulin resistance, nuclear FoxO1 increases follistatin (*Fst*), which provokes white adipose tissue (WAT) insulin resistance and lipolysis to deliver glycerol and non-esterified fatty acids to the liver for hepatic glucose production or re-esterification [101–104]. Severe and persistent starvation can trigger FOXO1-mediated hepatic insulin-like growth factor binding protein 1 (IGFBP-1) expression to reduce circulating IGF-I bioavailability and attenuate somatic growth [105]. In muscle, nuclear FOXO1 promotes autophagy that breaks down muscle protein for use by the liver to make glucose. Thus, reduced insulin signalling in skeletal muscle can underlie the loss of muscle mass and glycaemic levels during chronic insulin resistance [106].

Insulin-regulated glucose transport

Glucose transport is the prototype insulin response that is rate limiting for dietary glucose utilization by muscle and adipose [107, 108]. Members of the GLUT (sodium-independent, facilitated-diffusion glucose/hexose transporter) family are distinguished by substrate specificity and affinity, tissue distribution, and mechanism of regulation. GLUT4 is the principal insulin-responsive glucose transporter that is expressed in WAT, brown adipose tissue, skeletal muscle, and heart, where it plays a direct role in insulin-stimulated glucose influx and utilization.

The molecular mechanisms linking the insulin signal to increased glucose influx involves complex multistep coupling between the insulin signalling cascade and vesicle trafficking [107–109]. Under basal conditions, GLUT4 accumulates in a general recycling compartment that on sorting generates GLUT4 storage vesicles that form insulin-responsive vesicles that fuse with the plasma membrane in response to insulin (Figure 9.5) [107, 108, 110]. In addition to GLUT4, the storage vesicles contain other components, including sortilin that mediates GLUT4 retrieval from trans-Golgi network and sorting endosomes to form the GLUT4 storage vesicles [107].

Insulin acts at several sites to regulate GLUT4 translocation and recycling, including GLUT4 storage vesicle assembly, release from intracellular retention sites, transport and fusion at the plasma membrane, and return (Figure 9.5). AKT substrate of 160 kDa (AS160) and TBC1 domain family member 4 (TBC1D4) are GTPase-activating proteins that maintain their target Ras-associated proteins (RABs), including RAB8A, RAB10, RAB14, and others that regulate intracellular membrane flux, in an inactive GDP bound state under basal conditions [107, 108]. AKT phosphorylates and inhibits AS160 in adipose and TBC1Ds in muscle, which promotes RAB•GTP accumulation [111, 112]. GTP-loaded RAB8A and RAB14 (muscle) or RAB10 (adipose) facilitate translocation of GLUT4 storage vesicles to the plasma membrane (Figure 9.5) [107, 111]. AKT2 also phosphorylates and inactivates RAL•GAP, which leads to the accumulation and activation of RAL•GTP that binds to exocyst components, Sec5 and Exo70, to

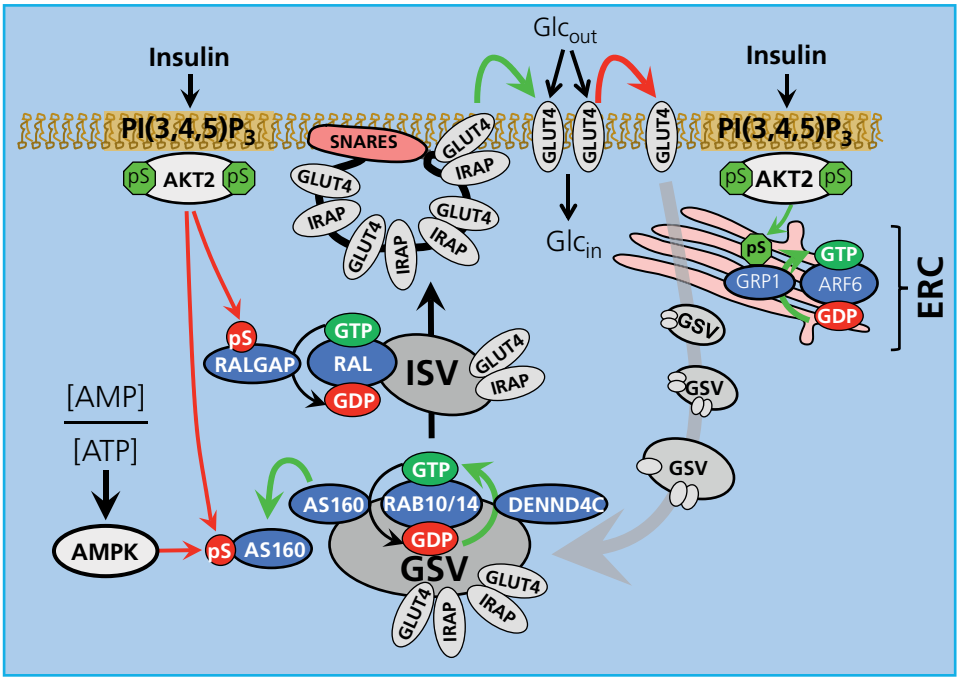

Figure 9.5 A mechanism of insulin-stimulated glucose transport by the PI3-kinase → AKT → AS160/RALGAP/GRP1 branch of the insulin signalling pathway in adipose or muscle. These AKT substrates mediate various steps of the assembly and trafficking of GLUT4 storage vesicles (GSVs). AKT → AS160/RALGAP promotes translocation of the GLUT4 storage vesicles to the plasma membrane. Endocytosis of GLUT4 is stimulated by AKT → GRP1•ARF6 signalling. Insulin-stimulated AKT promotes the accumulation of GLUT4-containing vesicles in the plasma membrane, which increases glucose influx.

tether insulin-responsive vesicles to the plasma membrane (Figure 9.5). Insulin can promote dissociation of a complex of diacylglycerol kinase-z and phosphatidylinositol 4-phosphate 5-kinase 1α (DGKz•PIP5K1α) from IRS1, which facilitates formation of the IRS1•PI3K complex to activate AKT and Rac family small GTPase 1 (RAC1) [107, 113]. RAC1 might promote AKT membrane compartmentalization or actin remodelling to enhance insulin-stimulated GLUT4 translocation [107, 108]. Thus, insulin-stimulated AKT contributes to translocation, docking, and fusion of GLUT4 vesicles with the plasma membrane [107, 111].

Insulin might regulate GLUT4 recycling back from the plasma membrane into an endocytic recycling compartment [114]. Formation of GLUT4 vesicles from the endocytic recycling compartment relies on a coat complex containing clathrin and ACAP1, an ARF6 GAP, which is recruited to endocytic recycling compartment membranes by GRP1, an ARF6-GEF [115]. Budding of GLUT4 storage vesicles from the endocytic recycling compartment is stimulated through the AKT-mediated phosphorylation of GRP1 [116]. Phospho-mimetic mutations in GRP1 increase plasma membrane GLUT4 localization in 3T3-L1 adipocytes, in large degree bypassing the GLUT4 vesicle retention mechanisms [116].

Heterologous regulation and insulin resistance

Nutrient excess causes insulin resistance, at least in part, because chronic insulin secretion inhibits proximal insulin receptor signals through feedback or heterologous inflammation [117–122]. Although elevated insulin defends against hyperglycaemia, it can increase hepatic lipogenesis, dyslipidaemia, WAT expansion, and hepatic steatosis [8]. Consequently, elevated circulating and hepatic lipids, including non-esterified fatty acids, diacylglycerol, and ceramides, can activate kinases directly or through inflammatory cascades to further inhibit proximal insulin signalling [106, 109, 123–127]. Nutrient excess also stimulates mTORC1-mediated feedback mechanisms that can inhibit insulin receptor → IRS1/IRS2 coupling and stability [128–130]. Regardless, physiological mechanisms that regulate the concentration and function of proximal insulin signalling components are not understood well enough to guide the development of efficacious and safe treatments.

Transcriptional control of IRS1

Several mechanisms regulate IRS1 transcription, including Wnt/β-catenin signalling [119, 131, 132]. Wnt3A or the constitutively active form of β-catenin increases the IRS1 gene and protein expressions, which decreases during suppression of the Wnt/β-catenin pathway. Moreover, chromatin immunoprecipitation analysis shows that T-cell factor 4 (TCF4), a component of the TCF/LEF lymphoid enhancer factor family, binds to the IRS1 promoter to stabilize Wnt/β-catenin signalling [133]. The TCF/LEF response elements are located between −7000 and −5966 in the mouse IRS1 promoter and transfection by siTCF4 reduces IRS1 mRNA and protein levels in H4IIE cells, suggesting that the β-catenin/TCF4 pathway can regulate IRS1 expression at the transcriptional level [119]. Wnt/β-catenin appears to regulate IRS1 expression in perivenous hepatocytes where lipogenesis predominates [119]. Wnt signalling agonists might modulate glucose homeostasis as a treatment for type 2 diabetes.

IRS1 expression is also regulated by transcriptional repressors, including transcription factor AP2β (AP2β), the p160 family of nuclear receptor coactivators p/CIP (p300/CBP/cointegrator-associated protein), and steroid receptor coactivator-1 (SRC1) [134, 135]. AP2β is expressed in adipose tissue where it promotes adipocyte hypertrophy, inhibits adiponectin expression, and enhances the expression of inflammatory adipokines such as interleukin 6 (IL-6) and C-C motif chemokine ligand 2 (MCP1) [134]. AP2β decreases IRS1 mRNA and protein concentration in adipocyte cell lines. Genome-wide association studies reveal AP2β as a candidate gene for the risk of obesity and type 2 diabetes, which might involve negative regulation of IRS1 expression [136]. By contrast, p/CIP and SRC1 serve as transcriptional coactivators for nuclear hormone receptors and certain other transcription

factors [137]. IRS1 expression increases on inactivation of p/CIP and SRC1 in mice, which increases glucose uptake and enhanced insulin sensitivity in WAT and skeletal muscle. Finally, muscle-specific TAZ (transcriptional coactivator with PDZ-binding motif) knockout mice display decreased IRS1 expression and insulin resistance [138]. Statins can reduce TAZ levels, which might reveal a mechanism of insulin resistance owing to decreased IRS1 expression; however, effects of statins on protein prenylation might also be involved [138].

Transcriptional control of IRS2

Unlike IRS1, IRS2 transcription is regulated by nutrient-sensitive factors – including cAMP response element binding protein (CREB) and its coactivator CREB regulated transcription coactivator 2 (CRTC2); FOXO isoforms; hypoxia-inducible factor-2α (HIF2α) encoded by EPAS1; nuclear factor of activated T cells (NFAT); PGC1A; sterol regulatory element binding protein 1 (SREBP1c); signal transducer and activator of transcription 3 (STAT3); and transcription factor E3 (TFE3) [139–142]. Multiple transcriptional mechanisms induce hepatic IRS2 expression during fasting, including nuclear FOXO that creates a direct feedback loop to augment insulin signalling during fasting and suppress it after a meal through AKT⟞ FOXO. Fasting or exercise also induce the CREB•CRTC2 transcriptional complex through glucagon signalling that increases expression of gluconeogenic genes along with IRS2 [140]. Moreover, glucagon acting through PGC1A can increase hepatic IRS2 expression while suppressing IRS1, which can finetune gluconeogenesis and hepatic glucose production during the fasting to feeding transition with a minimal effect on lipogenesis [142]. An E-box overlapping the FOXO site binds basic helix-loop-helix transcription factor E3 (TFE3), which converges with FOXO to promote IRS2 expression [143]; however, these elements also overlap with an SRE that binds sterol regulatory element binding transcription factor 1 (SREBF1), an important transcriptional activator of lipid synthesis [144]. Active hepatic SREBF1 increases during nutrient excess and chronic insulin stimulation, which decreases IRS2 expression to promote insulin resistance while promoting lipogenesis [145, 146]. HIF2α induces transcription of IRS2 in the hypoxic perivenous zone of the liver to restrain gluconeogenesis compared to other liver zones [119, 147]. Thus, IRS2 expression is highly integrated through multiple metabolic sensors to promote insulin sensitivity and metabolic homeostasis.

miRNA-mediated post-transcriptional regulation

MicroRNAs (miRNAs) are short (~20 nucleotides) non-coding RNA molecules that negatively modulate gene expression through their specific binding within the 3′UTR sequence of messenger RNA (mRNA) to inhibit translation or destabilize the target mRNA. Most of the proximal components of insulin signalling can be regulated in a tissue-specific way by miRNAs [148]. LET7 miRNA interferes with many proximal components, including type 1 IGF receptor, insulin receptor, IRS2, PIK3IP1, AKT2, TSC1, and RICTOR [149]. LET7 interference can be inhibited by the RNA binding proteins Lin28a and Lin28b, which block production of mature LET7 to increase translation of the insulin signalling components. LET7 associates with gigantism, puberty delay, and glucose homeostasis by modulating insulin → PI3K → mTOR signalling and insulin sensitivity [149].

Many other miRNAs display specificity against proximal insulin signalling components during metabolic challenge in various tissues. Hepatic miR-424-5p, miR-15b, miR-195, and miR-96 increase in mouse liver when fed a high-fat diet, which associates with less insulin receptor expression [150–153]. IRS1 and IRS2 are targeted by miRNAs in multiple peripheral insulin target tissues. miR-222 can suppress IRS1 in liver and adipose during high-fat diet and sucrose feeding [154]. Resistin upregulates miR-145 to inhibit IRS1 levels [155]. miR-29a and miR-29c suppress IRS1 expression in the muscle of individuals with type 2 diabetes or mice fed high-fat diets [156]. IRS1 can be downregulated in mouse endothelial cells by miR-126, which dysregulates angiogenesis [157]. Chronic angiotensin-II–induced hypertension can increase the expression of miR-487b in rat aorta, which suppresses IRS1 expression and promotes hypertension-induced cardiovascular disease and formation of aortic aneurysms owing to the loss of medial smooth muscle [158].

IRS2 expression is also suppressed by various miRNAs. The miR-126 targets IRS2 in pancreatic β cells, which can suppress islet growth [159]. Upregulation of miR-33b reduces hepatic IRS2 → AKT signalling while miR-135a reduces IRS2 → AKT signalling in the muscle of individuals with type 2 diabetes and *db/db* mice [160].

Finally, miR-26b appears to suppress PTEN to promote GLUT4 translocation in adipose and β-cell function during obesity [161]. Other proximal insulin signalling components are also modulated by various miRNAs, including SHIP2 (miR-205-5p), PDK1 (miR-375), AKT (miR-143⟞ ORP8 [oxysterol binding protein related 8]), PP2A (miR-19b, miR-429, miR-29, and miR-155), and type 1 IGF receptor [148]. Modulating miRNA expression *in vivo* might be a beneficial strategy to restore insulin sensitivity and treat some forms of type 2 diabetes [162].

Regulation of IRS signalling by Ser/Thr phosphorylation

IRS1 and IRS2 can be regulated through a complex mechanism involving phosphorylation of more than 50 potential phosphorylated Ser/Thr residues (pS/Ts) located in the long unstructured tail (Figure 9.6). Understanding how phosphorylated Ser/Thr residues regulate insulin signalling is challenging, because so many sites and mechanisms are involved [167]. Heterologous signalling cascades initiated by proinflammatory cytokines or metabolic excess, including tumour necrosis factor α (TNF-α), endothelin-I, angiotensin II, excess nutrients (free fatty acids, ceramides, amino acids, and glucose), or endoplasmic reticulum stress, are implicated in IRS1 and IRS2 phosphorylated Ser/Thr residues, which associate with less insulin-stimulated tyrosine phosphorylation [167]. Most IRS1/2 phosphorylated Ser/Thr residues are stimulated by the PI3K → Akt → mTOR cascade during insulin stimulation [163, 167]. Thus, IRS1/2 phosphorylated Ser/Thr residues are first and foremost a feedback mechanism that develops during chronic insulin stimulation, which can be co-opted by other agonists during metabolic stress to inhibit insulin signalling and dysregulate metabolic homeostasis (Figure 9.6) [167]. Thus, hyperinsulinaemia might be the important physiological mediator of insulin resistance in animals [5, 121].

Recently, AKT was shown to coordinate negative feedback by phosphorylating IRS1 and IRS2 on several serine residues [168]. AKT-mediated phosphorylation can deplete plasma membrane localized IRS1 and IRS2, which reduces their interaction with the insulin receptor. Reduced membrane-associated IRS protein decreases recruitment and activation of the PI3K, which reduces phosphatidylinositol(3,4,5)-triphosphate (PIP3) synthesis and insulin action. Two AKT-dependent phosphorylation sites in IRS2,

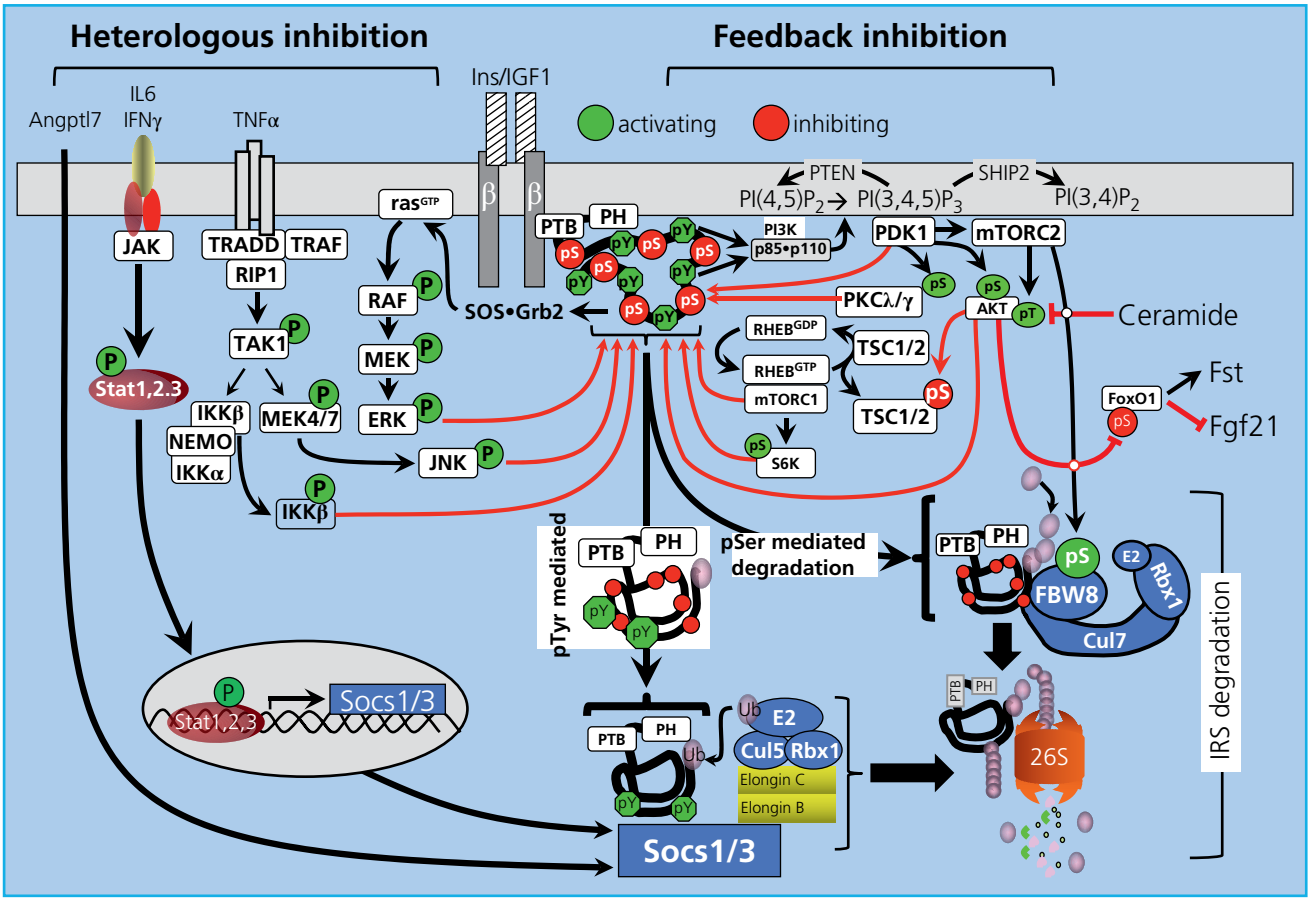

Figure 9.6 Schematic diagram of heterologous and feedback regulation of insulin signalling. Various kinases in the insulin signalling cascade mediate feedback inhibition of IRS, including PKB, mTOR, S6K, ERK, AKT, and atypical PKC isoforms [163]. Other kinases activated by heterologous signals, including lipids such as ceramide, are also involved. Serine phosphorylation of IRS1 can recruit CRL7, which can promote ubiquitinylation and degradation of IRS1 through the 26S proteasome. Many proinflammatory cytokines cause insulin resistance through SOCS1 or SOCS3 that targets phosphotyrosine-containing proteins like IRS1 or IRS2 for ubiquitinylation by a BC-containing ubiquitin ligase (E3) and degradation [164–166].

mouse S303 and S573 (human S306 and S577), might mediate this negative feedback, but other sites can be involved [163]. These findings establish a novel mechanism by which AKT can feedback to attenuate insulin-stimulated PIP3 production, providing a mechanism to modulate insulin signalling independent of other signalling pathways.

Mouse S307^{IRS1} (human S312^{IRS1}) is one of the best-studied pS/T in IRS1, which is often used as barometer of insulin resistance [167]. Insulin can promote pS307^{Irs1} phosphorylation through the PI3K → AKT → mTORC1 → S6K1 (Figure 9.6) [163]. In mice, free fatty acids promote pS307^{IRS1}, but insulin resistance and hyperinsulinemia are not excluded as the cause [167]. c-Jun N-terminal kinase (JNK1) or mTORC1 activated in obese mice promotes pS307^{IRS1} and other sites [169, 170]. Although most if not all cell-based investigations support an inhibitory role for pS307^{IRS1}, mouse-based experiments are less convincing. Genetic knock-in to replace S307^{IRS1} with alanine (A307^{IRS1}) increases fasting insulin and glucose levels while decreasing p110^{PI3K} binding to IRS1 PI3K [171]. During the high-fat diet, A307^{IRS1} mice exhibit more severe glucose intolerance and higher fasting insulin than control S307^{Irs1} mice. In mice, pS307^{Irs1} and other phospho-S/Ts might attenuate the detrimental effects of compensatory hyperinsulinaemia to maintain some relative insulin sensitivity [171]. More work is needed to establish the mechanisms involved.

Regulation of IRS degradation

Proteasome-mediated degradation regulates many biological processes including signal transduction, gene transcription, and cell cycle progression. Proteins targeted for destruction by the 26S proteasome are polyubiquitinylated by various complexes comprising a ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2), and ubiquitin-protein ligase (E3) [172]. IRS1 and IRS2 can be polyubiquitinylated during chronic inflammatory states, nutrient excess, and hyperinsulinaemia through various tissue-specific mechanisms [173]. The first pathway discovered involves suppressor of cytokine signalling 1 and 3 (SOCS1/3), which binds to IRS1 through its SH2 domain and to a ubiquitin E3 ligase through its SOCS box (Figure 9.6) [174, 175]. Mutations in the SOCS box prevent ubiquitinylation and degradation of IRS1 or IRS2 [174], and inhibition of SOCS1/3 expression by anti-sense oligonucleotides improves insulin sensitivity in obese and diabetic mice [176]. Cytokines like interferon γ (INFγ) or IL-6 activate Janus kinases (JAK) promote phosphorylation and dimerization of signal transducer and activator of transcription (STAT) factors, which migrate into the nucleus to induce SOCS1/3 expression (Figure 9.6) [177]. Angiopoietin-like 7 (Angptl7) also increases SOCS3 during obesity [178]. Thus, SOCS-mediated polyubiquitination of IRS1 or IRS2 can promote insulin resistance and glucose intolerance during infection, inflammation, or metabolic stress.

Other mechanisms of IRS degradation are coordinated by pS/T on IRS1 or IRS2. Cullin-RING E3 ubiquitin ligase 7 (CRL7) mediates IRS1 degradation downstream of pS/T generated by the PI3K → AKT → mTORC1 cascade [179]. CRL7 complex contains cullin 7 (CUL7), a molecular scaffold that assembles F-box/WD repeat-containing protein 8 (FBW8) to recruit phosphorylated substrates, and RING-box protein 1 (Rbx1), associated with an E2 conjugating enzyme (Figure 9.6). FBW8 apparently binds to IRS1 through pS/T residues generated by the mTORC1 → S6K cascade, including human $pS307^{IRS1}$, $pS312^{IRS1}$, and $pS527^{IRS1}$, but possibly others, to mediate polyubiquitinylation of IRS1 that progresses to degradation (Figure 9.6) [179, 180]. This regulatory mechanism might be engaged during nutrient excess or hyperinsulinaemia, as it depends on chronically hyperactivated mTORC1 → SK6 [180].

Chronic consumption of high-calorie diets upregulates Cbl proto-oncogene B (CBLB), a RING-type E3 ubiquitin ligase that belongs to the casitas B-lineage lymphoma family of proteins [106]. CBL proteins share a conserved NH_2-terminal region containing a tyrosine kinase binding domain and a RING-finger domain to facilitate E3 ubiquitin ligase activity. Calorie excess induces carbohydrate-responsive element-binding protein (ChREBP) and SREBP1c, which upregulates myostatin in murine muscle to induce CBLB expression that drives insulin resistance through the polyubiquitinylation and degradation of IRS1 [181].

Regulation by protein and lipid phosphatases

Phosphatases modulate insulin signalling by dephosphorylating key proteins or lipids in the signalling cascade, including PTP1B (tyrosine-protein phosphatase non-receptor type 1, PTPN1), PTPN2 (tyrosine-protein phosphatase non-receptor type 2, TCPTP), protein phosphatase 2A (PP2A), protein phosphatase 1 (PP1), phosphatase and tensin homolog (pTEN), tensin-like C1 domain-containing phosphatase (C1-TEN), and Src homology 2 domain-containing inositol 5′-phosphatase 2 (SHIP2). PTP1B and PTPN2 are related phosphotyrosine phosphatases that dephosphorylate various receptor tyrosine kinases, including the A-loop of the insulin receptor [182]; however, their biological effects can be distinct owing to different time courses and tissue expression [183]. $PTP1B^{-/-}$ mice display increased insulin sensitivity, lower circulating insulin concentrations, and decreased pancreatic β-cell mass [184]. Physiologically, both PTP1B and PTPN2 can be inactivated by reactive oxygen species generated during insulin stimulation [185, 186]. In pancreatic β cells, PTP1B attenuates the IRS2 → PI3K → AKT cascade that is important for growth, function, and survival of these cells [187]. Thus, inactivation of PTP1B can maintain β-cell mass in mice lacking IRS2, which prevents the early onset of diabetes [187]. Regardless, without IRS2 even the $IRS2^{-/-}$•$PTP1B^{-/-}$ mice lose β-cell mass between 8 and 9 months of age, as IRS1 signalling fails to compensate. PTP1B also inhibits leptin signalling (LepRb → JAK2) as it dephosphorylates JAK2. PTPN2 dephosphorylates JAK1/3 but not JAK2 [182]. Central nervous system inhibition of PTP1B can protect against obesity, while peripheral inhibition of PTP1B promotes glucose tolerance [188]. Inhibition of PTP1B or TCPTP in the brain, or specific hypothalamic neurons, promotes insulin and leptin signalling and prevents diet-induced obesity, type 2 diabetes, and non-alcoholic fatty liver disease [189]. Regardless, targeting PTP1B and TCPTP for treatment has been problematic due to challenges in targeting the inhibitor to specific tissues; however, intranasal targeting of PTP1B and TCPTP can increase leptin and insulin sensitivity and promote weight loss by repressing feeding and increasing energy expenditure [190].

pTEN is a potent negative regulator of insulin action and cellular proliferation and is a frequently mutated gene in human cancer [191, 192]. pTEN attenuates insulin signalling by dephosphorylating $PI(3,4)P_2$ and $PI(3,4,5)P_3$ at the 3-position, which reduces the recruitment and activation of PDK1, AKT, and others (Figure 9.6) [192]. pTEN heterozygosity can increase peripheral insulin sensitivity in $Irs2^{-/-}$•$Pten^{+/-}$ mice and normalizes glucose tolerance, as the small islets in these mice produce enough insulin until death between 10 and 12 months age. These experiments highlight the complex relation between nutrient homeostasis, insulin sensitivity and secretion, and cancer that can emerge in rodents and humans without full pTEN activity.

Phosphatidylinositol-3,4,5-trisphosphate 5-phosphatase (SHIP2) encoded by the *INPPL1* gene attenuates insulin signalling by dephosphorylating the 5′-position of PtdIns(3,4,5) (Figure 9.6). Several genetic studies link SHIP2 to metabolic disorders, showing that polymorphisms in *INPPL1* may contribute to the pathogenesis of the metabolic syndrome, hypertension, and type 2 diabetes [193]. Despite this complexity, SHIP2 inhibition might have therapeutic value. Metformin might increase insulin sensitivity by inhibiting SHIP2, which enhances glucose uptake while protecting renal podocytes from apoptosis in diabetic rodent models [194].

Phosphoserine-directed phosphatases, including PP2A and PP1, have complex effects depending on substrate targeting. PP2A is a widely expressed pSer/pThr protein phosphatase that forms a heterotrimeric complex with scaffold and regulatory subunits to target various subcellular locations and substrates [195]. PP2A can be a negative regulator of insulin's metabolic signalling by dephosphorylating and inactivating AKT or dephosphorylating and activating GSK3β [196, 197]. PP2A also targets pS/Ts in IRS1, which stabilizes IRS1 for tyrosine phosphorylation to enhance insulin signalling [198, 199]. PP1 also targets and dephosphorylates IRS1. Phosphoproteomic analysis of L6 skeletal muscle cells reveals the interaction of myosin phosphatase targeting subunit 1 (MYPT1), a targeting subunit of protein phosphatase 1cβ (PP1cβ) with IRS1 [200]. Activation of the MYPT1•PP1 complex by PKA promotes dephosphorylation of serine residues in IRS1 to increase tyrosine phosphorylation and stimulate the PI3K → AKT cascade [201].

Mouse genetics reveal tissue-integrated insulin signalling

During the past 25 years, investigators used genetically manipulated mice to understand the molecular and integrated physiology of insulin action. Proximal insulin signalling steps are similar in all tissues, whereas the downstream effects and heterologous regulation can be tissue specific (Figure 9.7). For example, in liver, postprandial Pi3k → Akt inhibits FOXO1, which regulates hundreds of genes including increasing genes for *de novo* lipogenesis (↑*Srebf1*, ↑*Gck*, ↑*Fasn*) and inhibiting genes for hepatic glucose production (↓*Pck1*, ↓*G6pc*) [103, 118, 202, 203]. In adipose, Pi3k → Akt activates phosphodiesterase 3β (PDE3β) to reduce cAMP and suppress lipolysis, whereas it inhibits AS160 to stimulate glucose influx (Figure 9.7) [204–206]. In muscle, Pi3k → Akt inhibits protein degradation while stimulating protein and glycogen synthesis and glucose oxidation (Figure 9.7) [207, 208]. The Akt → mTorc1 branch

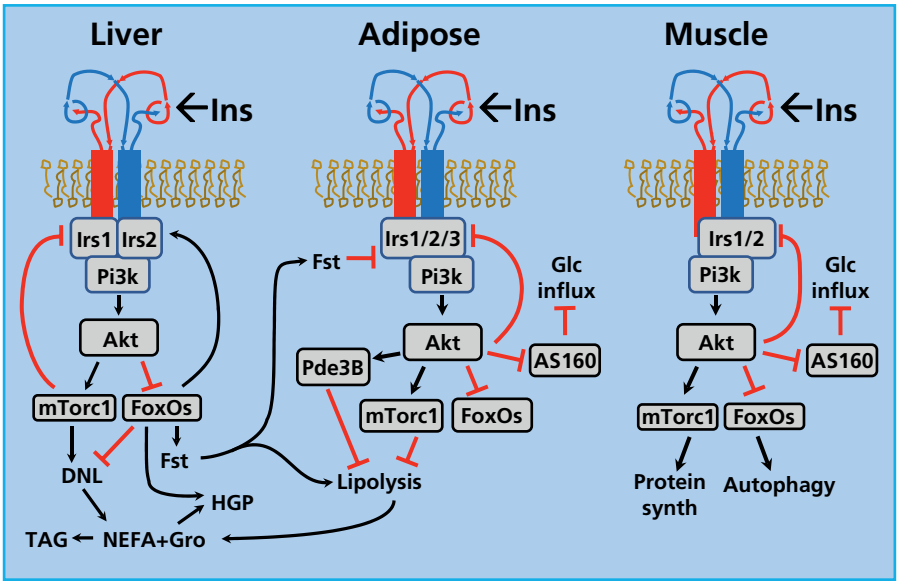

Figure 9.7 Tissue-specific insulin signalling. The insulin receptor is autophosphorylated on multiple tyrosine residues, allowing the docking and activation of multiple signalling molecules, most notably insulin receptor substrates (IRS) proteins. This in turn activates phosphatidylinositol-3-kinase (PI3K) and AKT to mediate the increases in glucose uptake and metabolism as well as changes in protein and lipid metabolism. While the general pathway is similar in all tissues, the final biological effects are specialized to the roles of insulin in liver (inhibits hepatic glucose production and stimulated *de novo* lipogenesis), adipose (inhibits lipolysis and stimulates glucose influx), and muscle (inhibits autophagy and stimulates proteins synthesis and glucose influx).

is common to all tissues and stimulates anabolic pathways, including sterol regulatory element-binding factor 1 (Srebp1c)–mediated hepatic *de novo* lipogenesis (Figure 9.7) [209–212]. During fasting or insulin resistance, nuclear FoxO1 induces Follistatin (Fst), which provokes WAT insulin resistance and lipolysis to deliver glycerol and non-esterified fatty acids to the liver for hepatic glucose production or re-esterification (Figure 9.7) [101–104].

Since regulatory tissue cross-talk complicates the analysis of whole-body gene deletion, Cre-loxP technology or specific viral-mediated expression has been used to investigate the role of IR → IRS → AKT ⟞ FOXO1 signalling in specific tissues [213,214]. Even tissue-specific gene deletion has limitations, as insulin signalling is rarely lost completely in common metabolic disease. Moreover, targeted deletions still influence metabolic regulation throughout the organism owing to crosstalk by secreted peptides, metabolites, or neuronal interconnections [103,215]. Regardless, Cre-loxP technology continues to be valuable to dissect the insulin signalling cascades.

Systemic insulin receptor signalling cascade

Mice lacking the insulin receptor have nearly normal size but less adipose tissue mass at birth, and die a few days after birth with severe hyperglycaemia, pancreatic β-cell failure, and ketoacidosis [216]. Thus, insulin → insulin receptor signalling is essential for postnatal nutrient homeostasis [217]. Insulin receptor–deficient mice can be rescued genetically by transgenic expression of the insulin receptor in the brain, liver, and pancreatic β cells [218]. Unlike mice, humans with rare mutations leadings to a lack of functional insulin receptors display intra-uterine growth retardation, failure to thrive, and hypoglycaemia for weeks until hyperglycaemia ensues [217]. This paradox might involve limited availability of gluconeogenic substrates or extreme hyperinsulinaemia that might activate enough IGF-I receptors to generate some insulin-like actions [219].

Systemic IRS1 or IRS2 deletion suggests that each substrate can display unique signalling properties in various tissues. The signalling specificity probably arises from different expression levels, receptor coupling, or feedback regulation [220]. Systemic deletion of IRS1 produces small insulin-resistant mice with nearly normal glucose homeostasis owing to β-cell expansion and life-long compensatory hyperinsulinaemia [221]. These results suggest that IRS1 is the principal mediator of IGF-I–regulated body growth, but is not essential for β-cell growth. By contrast, mice lacking IRS2 display nearly normal body growth and even gain fat mass; however, male $IRS2^{-/-}$ mice develop life-threatening diabetes after 8 weeks of age owing to the progressive loss of β-cell mass that disrupts compensatory hyperinsulinaemia [222]. Female mice develop diabetes more slowly, and many but not all develop severe hyperglycaemia by 6 months [223]. Thus, other mechanisms might promote β-cell growth and survival in females.

Compound deletion of IRS1 and IRS2 appears to be embryonic lethal; however, littermates retaining one allele of IRS1 ($IRS1^{+/-}$•$IRS2^{-/-}$) or one allele of IRS2 ($IRS1^{-/-}$•$IRS2^{+/-}$) can be born alive [224]. $IRS1^{+/-}$•$IRS2^{-/-}$ mice develop severe fasting hyperglycaemia and die by four weeks of age as β-cells fail to grow or survive. By contrast, $IRS1^{-/-}$•$IRS2^{+/-}$ mice have a very small body but have normal or elevated β-cell mass to secrete enough insulin for glucose tolerance [224]. Thus, IRS1 and IRS2 are essential for development and nutrient homeostasis, and some IRS2 is essential for β-cell growth, function, and survival.

Hepatic insulin receptor⟞ FOXO1 signalling

The liver is an important site of insulin action that plays a role in systemic glucose and lipid homeostasis [213]. LIRKO ($IR^{L/L}$•Cre^{Alb}; hepatic albumin Cre driver) mice display moderately elevated fasting glucose and severe post-prandial hyperglycaemia and glucose intolerance [225]. LIRKO mice also develop severe hyperinsulinaemia owing to a combination of increased insulin secretion to control hyperglycaemia and reduced hepatic insulin degradation [226]. LIRKO mice display reduced levels of circulating free fatty acids and triglycerides on ordinary chow diets [213,225]; however, on an atherogenic diet LIRKO mice develop dyslipidaemia that can progress to atherosclerosis [227]. Insulin receptor deletion dysregulates hundreds of hepatic genes, including reduced glucokinase and hexokinase 4 (*GCK*) and elevated phosphoenolpyruvate carboxykinase 1 (*PCK1*), glucose-6-phosphatase, catalytic subunit (*G6PC*), and pyruvate kinase (*PK1*) [213,225]. Chronic hyperinsulinaemia in LIRKO mice exacerbates peripheral insulin resistance, while streptozotocin injections to reduce insulin secretion improve peripheral insulin resistance but fail to suppress hepatic glucose

production [228]. Thus, heterologous mechanisms dysregulated by hepatic insulin resistance – including the systemic effects of hyperinsulinaemia – might exacerbate hepatic glucose production through indirect mechanisms that promote adipose insulin resistance and delivery of excess glycerol and non-esterified fatty acids to the liver for hepatic glucose production [103, 229, 230].

For over a decade, we have modelled hepatic insulin resistance by genetic inactivation of hepatic IRS1 and IRS2 in LDKO ($Irs1^{L/L}$•$Irs2^{L/L}$•Cre^{Alb}) mice [103, 118, 202, 203]. LDKO mice display unsuppressed hepatic glucose production, hyperinsulinaemia, glucose intolerance, and diabetes [103, 118, 202, 203]. At first, these results suggested that hepatic IRS1/2 mediates systemic nutrient homeostasis through hepatic insulin signalling; however, white and brown adipose tissue and skeletal muscle are also insulin resistant in LDKO mice, suggesting that dysregulated hepatic metabolism manifests systemically [103, 231]. Remarkably, metabolic health is restored upon hepatic inactivation of FoxO1 in LTKO (LDKO•$FoxO1^{L/L}$) mice, even though the liver is mechanistically unresponsive to insulin [103, 118, 202, 203, 231]. These findings are confirmed and extended with compound hepatic-specific LIRKO•$FoxO1^{L/L}$ mice or $Akt1^{L/L}$•$Akt2^{L/L}$•$FoxO1^{L/L}$•Cre^{Alb} mice [80, 232–234].

Genetic disruption of hepatic FOXO1 substantially normalizes the expression of hundreds of dysregulated hepatic genes [80, 202]. Within such mice, FOXO1-dependent gene expression or metabolites generated in hepatocytes and circulating systemically could promote peripheral insulin resistance and the delivery of metabolic intermediates to the liver, including excess glycerol and free fatty acids from adipose tissue [235]. Comprehensive analyses of the LDKO and LTKO mice reveals that *Fst*, best known for its modulation of transforming growth factor (TGF)-β superfamily members Activin and Myostatin [236, 237], is a key FOXO1-dependent hepatokine that promotes WAT lipolysis during hepatic insulin resistance [103]. Thus, while failing to restore hepatic insulin signalling *per se*, disruption of hepatic FOXO1 in LTKO mice and similar models might restore glucose tolerance by normalizing hepatokine secretion [202, 232, 233, 238].

Insulin signalling and glucose homeostasis in skeletal muscle

Skeletal muscle is a major site for utilization and storage of ingested glucose after a meal [8]. Defective insulin signalling at the level of the insulin receptor and IRS1-associated PI3K is associated with reduced insulin-stimulated muscle glucose storage. Regardless, some but not all aspects of metabolic disease emerge on deletion of skeletal muscle insulin receptor in MIRKO ($IR^{L/L}$•Cre^{Mck}; muscle creatine kinase Cre driver) mice [213, 239]. Unexpectedly, hyperglycaemia and hyperinsulinaemia never develop in MIRKO mice, while they do develop mild obesity with elevated circulating free fatty acids and triglycerides. Moreover, deletion of the insulin receptor and type 1 IGF receptor in MIGIRKO mice ($IR^{L/L}$•$IGFIR^{L/L}$•Cre^{ACTA1}; human skeletal muscle actin Cre driver) leads to them displaying more than 60% less muscle mass while glucose and insulin tolerance remain normal, owing, at least in part, to increased basal glucose uptake [240]. Consistent with these results, MDKO ($Irs1^{L/L}$•$Irs2^{L/L}$•Cre^{Mck}) mice also fail to develop hyperglycaemia and glucose intolerance during progressive and fatal skeletal and cardiac muscle autophagy [207]. Akt phosphorylation is completely lost in MDKO mice, suggesting that insulin receptor/type 1 IGF receptor signalling is its major agonist [207]. Isolated skeletal muscles from MDKO mice show elevated basal but absent insulin-stimulated glucose uptake, while glucose metabolism shifts to lactate production, which elevates the AMP/ATP ratio, activating AMP-activated protein kinase (AMPK). Activated AMPK can promote phosphorylation of AS160/TCB1D4 and TCB1D1 to increase translocation of GLUT4 to the cell surface, which increases glucose uptake during complete insulin resistance [207].

By contrast to the effect of complete muscle insulin resistance, muscle-specific deletion of GLUT4 dysregulates glucose homeostasis and promotes systemic insulin resistance [241]. MG4KO ($Glut4^{L/L}$•Cre^{Mck}) mice develop hyperglycaemia, glucose intolerance, and insulin resistance by 8 weeks of age [242]. These mice also display dysregulated glucose metabolism in adipose and liver. Hyperglycaemia owing to diminished muscle glucose utilization appears to drive heterologous insulin resistance, because normalization of circulating glucose by kidney excretion can restore insulin action in adipose and liver [241, 243].

Adipose insulin signalling

Insulin signalling promotes adipogenesis, glucose influx, lipid synthesis, and anti-lipolysis in WAT [108, 109]. WAT is important for the storage of post-prandial glucose as triglyceride and the secretion of signalling factors that regulate appetite and energy homeostasis [5, 244]. WAT mainly expresses IRB without a detectable type 1 IGF receptor; however, both receptors play a role in adipogenesis from progenitor cells. Interpretation of the genetic deletion of adipose insulin receptor is complicated by the Cre-drivers used to generate the various experimental mice, including Cre^{aP2} (FIRKO mice; fatty acid binding protein 4 Cre driver) verses Cre^{Adipo} (F-IRKO mice; adiponectin Cre driver) [245, 246]. FIRKO mice display variable recombination efficiency in fat depots with some off-target events, whereas F-IRKO mice have more efficient insulin receptor deletion across fat depots with few or no off-target effects [247]. With respect to these caveats, FIRKO mice display beneficial metabolic effects, including systemic insulin sensitivity, normal glucose tolerance, and less fat mass on ordinary chow diets [245]. FIRKO mice also have a longer lifespan, suggesting that leanness and insulin sensitivity are associated with longevity [248]. By contrast, F-IRKO mice display lipodystrophy with hepatomegaly, steatosis, and increased enzymes of *de novo* lipogenesis [246]. F-IRKO mice develop a full spectrum of non-alcoholic fatty liver disease that can progress to non-alcoholic steatohepatitis, fibrosis, and liver dysplasia, which is more in line with the expected effects of adipose insulin resistance [5]. These phenotypes are exacerbated on compound deletion of the insulin receptor and type 1 IGF receptor by Cre^{Adipo}, which promotes lipodystrophy of white and brown adipose tissue accompanied by diabetes, insulin resistance, increased β-cell mass, and ectopic lipid accumulation [247]. Thus, the insulin receptor appears to be essential for the formation and maintenance of WAT, whereas both insulin receptor and type 1 IGF receptor contribute to brown adipose tissue mass development and thermogenesis.

Insulin-regulated GLUT4-mediated glucose transport is rate limiting for glucose influx into white and brown adipose tissue under normal glucose and insulin concentrations. GLUT4 translocation to the plasma membrane is extremely sensitive to insulin in adipose, as submaximal activation of AKT2 can stimulate glucose transport. Before high-fat diet–induced insulin resistance inhibits AKT phosphorylation, GLUT4 translocation is strongly inhibited, suggesting that decreased glucose utilization might reside

downstream of proximal insulin receptor and AKT activity [5]. Increased adipose GLUT4 expression can rescue systemic insulin resistance of mice fed the high-fat diet [249].

Adipose triacylglycerol storage is regulated by circulating factors with opposing effects on lipolysis – including β-adrenergic receptors (βAR1/2/3) and insulin. Activation of βAR1/2/3 stimulates cAMP production to promote PKA-mediated phosphorylation of perilipin 1 (PLIN1), which releases abhydrolase domain containing 5, lysophosphatidic acid acyltransferase (ABHD5) to fully activate patatin like phospholipase domain containing 2 (ATGL/PNPLA2), hydrolysing one fatty acid from triacylglycerol [250]. PKA also phosphorylates hormone-sensitive lipase (HLS) to promote its translocation to PLIN1 to hydrolyse fatty acids from diacylglycerol and produce monoacylglycerol [251]. Insulin inhibits lipolysis to promote fatty acid storage as triacylglycerol in adipose lipid droplets [251,252]; however, the mechanism is only partly understood, as the deletion of AKT2 only partly impairs the ability of insulin to suppress lipolysis [204,251]. Regulated lipolysis is critical as it controls the delivery of non-esterified fatty acids and glycerol to the liver, which stimulates hepatic glucose production [5,109]. Insulin inhibits lipolysis by hydrolysing cAMP through an uncertain mechanism. Originally, AKT was thought to activate PDE3β by phosphorylation; however, the direct phosphorylation of PDE3B by AKT might not be required [204]. Instead, AKT phosphorylates α/β hydrolase domain-containing protein 15 (ABHD15), which binds and stabilizes PDE3B for the anti-lipolytic action of insulin [205, 206, 251].

IRS2 as a gateway to β-cell function

The capacity of pancreatic β cells to maintain glucose homeostasis during chronic physiological and immunological stress is important for cellular and metabolic homeostasis [253]. Pancreatic β cells have a special place in nutrient homeostasis as the unique source of insulin that also require insulin signalling for growth, function, and survival (Figure 9.8). Since β cells are always exposed to insulin and IGFs, the proximal signalling cascade appears to be regulated through multifactor transcriptional control of IRS2 – including FOXO1/3, NFAT, and CREB•CRTC2 (Figure 9.8) [254]. In β cells, FOXO can account for as much as 80% of IRS2 expression [255]. Since the IRS2 → PI3K → AKT cascade phosphorylates and inhibits FOXO, insulin or IGF-I has inhibitory effects on FOXO-mediated transcription of IRS2. Since β-cell mass and function must be protected or expanded during chronic nutrient excess, other mechanisms, especially glucose-stimulated Ca^{2+} influx and cAMP production, promote IRS2 expression to avoid progressive β-cell failure (Figure 9.8). In addition to its immediate role in insulin secretion, glucose → Ca^{2+} release activates calcineurin, which dephosphorylates NFAT to facilitate its entry into the nucleus, where it induces expression of IRS2 and other genes (Figure 9.8) [256]. Glucose, glucagon-like peptide 1 (GLP-1), and other G-protein–coupled receptor (GPCR) agonists also increase cAMP in β cells, which has many important effects, including the activation of CREB•CRTC2 that promotes IRS2 transcription [257,258]. Through this mechanism, the role of insulin or IGF-I to regulate signalling in β cells is replaced by indirect control through glucose, incretins, or neuronal signals, the physiologically relevant regulators of pancreatic β-cell function (Figure 9.8). IRS2 expression through these mechanisms maintains PDX1 action, which is essential for β-cell growth, function, and survival [259]. Compounds that augment IRS2 expression might provide treatments for β-cell failure during insulin resistance and the progression of type 2 diabetes [253].

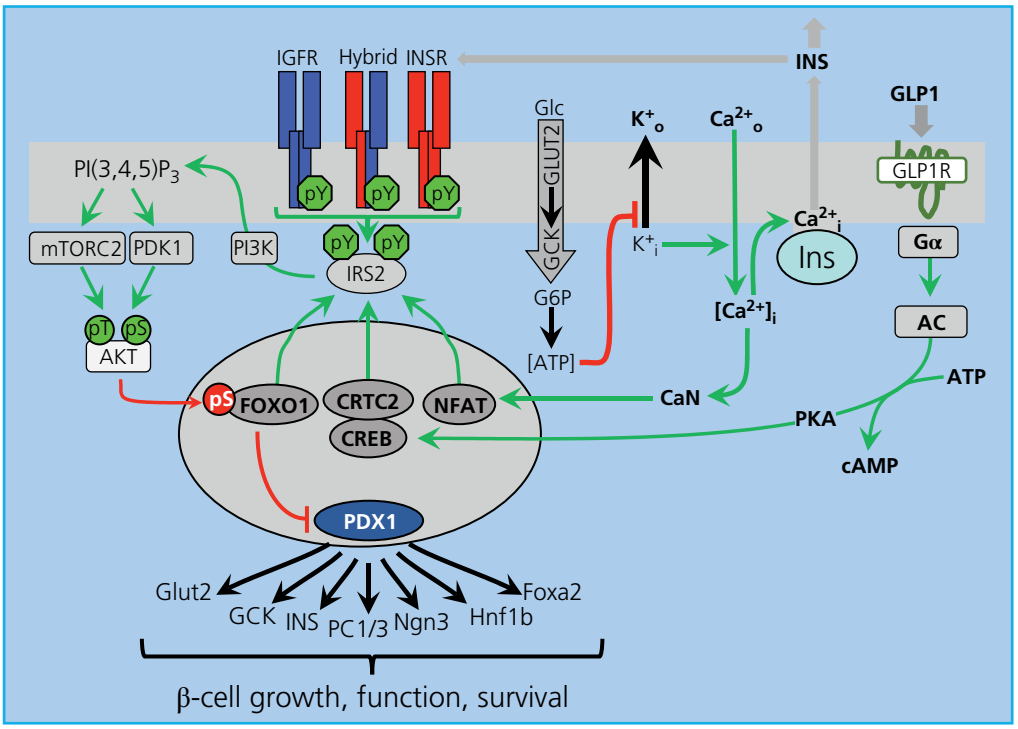

Figure 9.8 The integrative role of IRS2 signalling in pancreatic β-cell function. The diagram shows the relation between the IRS2 branch of the insulin signalling pathway and upstream and downstream mechanisms regulating β-cell growth and function. Since the insulin receptor and type 1 IGF receptor are constitutively active in β cells, activation of GLP1 → cAMP → PKA → CREB, glucose → Ca^{2+} → CRTC2, and calcineurin → NFAT induces IRS2 expression to stimulate the PI3K → AKT cascade, which places β-cell growth, function, and survival under the control of glucose and natural or synthetic incretins.

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10 Central Control of Glucose Homeostasis

Kimberly M. Alonge, Kendra L. Francis, Nicole E. Richardson, and Michael W. Schwartz

UW Medicine Diabetes Institute, Department of Medicine, University of Washington, Seattle, WA, USA

Key points

- Working in cooperation with pancreatic islets, the brain helps to establish the biologically defended level of glycaemia (BDL_G) by influencing both insulin-dependent and -independent glucose disposal.
- Whereas insulin-dependent mechanisms predominate in the post-prandial state, control of the basal glucose level depends largely on insulin-independent glucose disposal. The brain can potently influence both processes.
- Type 2 diabetes pathogenesis involves β-cell dysfunction leading to impaired insulin secretion, in concert with reductions of both insulin sensitivity (usually associated with obesity) and insulin-independent glucose disposal. These defects combine to raise the BDL_G out of the normal range.
- In both humans and animal models, obesity and type 2 diabetes are associated with pathology affecting the mediobasal hypothalamus, a key brain area for glucose homeostasis. One example of this pathology is the activation of mediobasal hypothalamus glial cells, referred to as *reactive gliosis*.
- In pre-clinical diabetes models, therapeutic interventions targeting the hypothalamus are capable of restoring the BDL_G to the normal range.
- Investigation into the therapeutic potential of targeting glucoregulatory neurocircuits to induce sustained diabetes remission in humans is a research priority.

Among many biological variables that are maintained within narrow physiological limits in healthy individuals is the circulating glucose level, and this regulation is achieved through a set of highly coordinated responses that are engaged when the blood glucose level deviates from its biologically defended range. In this chapter we focus on mechanisms underlying the *biologically defended level* of glycaemia (BDL_G), including the roles played by the brain, pancreatic islets, liver, and other tissues, and on how dysfunction of this control system results in type 2 diabetes and related disorders of glucose metabolism. Like other homeostatically defended variables (e.g. body fat mass, blood glucose, body temperature, blood pressure), the BDL_G is established by a highly integrative feedback control system that balances the sum total of all relevant inputs and outputs that influence glucose appearance and removal. Growing evidence places cooperation between brain and pancreatic islets at the centre of this regulatory process, and suggests that dysfunction of either can contribute to the pathogenesis of type 2 diabetes.

Evolutionary considerations

In 1849, Claude Bernard, a French physiologist and professor of medicine at the Collège de France, introduced the idea of a multiorgan *milieu interne* in the control of complex homeostatic systems [1]. Bernard was also the first to hypothesize that, like most other homeostatic control systems, the brain plays a key role in glucose homeostasis. Given the brain's reliance on glucose as its main fuel source, it makes teleological sense for the brain to have evolved mechanisms that ensure a continuous supply of glucose.

Although underappreciated until recently, this view is consistent with evidence that brain control of glucose homeostasis emerged early in the course of evolution. This evidence is based in part on studies in the fruit fly *Drosophila melanogaster* demonstrating that both the systemic glucose level (in haemolymph) and glucose-induced secretion of Drosophila insulin-like peptides (DILPs) (the insulin homologue in flies) are governed by a single pair of glucose-sensing neurons (Figure 10.1) [2]. Silencing of these neurons causes insulin secretion to decrease and systemic glucose levels to rise, even though the insulin-secreting cells themselves are not directly impacted [2]. Such findings suggest the following:

- These glucose-sensing neurons are essential for normal glucose homeostasis in flies.
- Glucose sensing developed in neurons before being co-opted by pancreatic β cells in the control of insulin secretion in mammals.
- Glucose homeostasis over the course of evolution originated as a process governed by the brain, with insulin secretion lying downstream of brain glucose sensing.

Although glucose homeostasis in mammalian systems is far more complex, many lines of evidence suggest that elements of the *Drosophila* model have been retained over the course of mammalian evolution (Figure 10.1).

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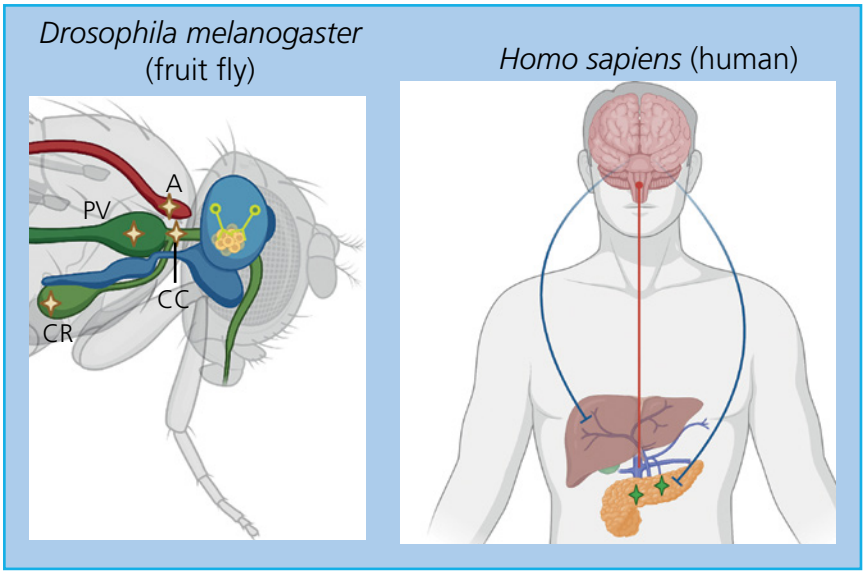

Figure 10.1 Evolution of brain glucose sensing. The brain of the fruit fly *Drosophila melanogaster* contains a pair of glucose-sensing neurons (light green) that, upon stimulation by glucose, promote secretion of insulin-like peptide-2 (DILP-2; yellow star) from insulin-producing cells (IPCs; yellow) into peripheral tissues (corpora cardiaca [CC], aorta [A], PV [proventriculus], and crop [CR]) to promote glucose lowering. Although the system is more complex and less well understood, the human brain is hypothesized to receive afferent information regarding the circulating glucose level via a distributed system that includes neurons (and perhaps glial cell types) located in circumventricular organs of the brain (such as the hypothalamic median eminence) as well as glucose-sensing neurons supplying peripheral blood vessels (e.g. portal vein, red line). In response to this afferent input, glucoregulatory neurocircuits influence glucose homeostasis via autonomic output (blue lines) to multiple tissues, including liver (to control hepatic glucose production and uptake) and pancreas (to control secretion of insulin and glucagon [green star]). Source: Figure generated using http://Biorender.com.

Overview of brain control of glucose homeostasis in normal physiology

Following a meal, ingested glucose and other nutrients enter the circulation from the gastrointestinal tract, eliciting a multitude of responses that both increase glucose disposal and inhibit endogenous glucose production to minimize the resultant blood glucose excursion. Insulin is a key mediator of these responses, promoting glucose disposal into muscle, fat, and other insulin-sensitive tissues, while simultaneously restraining endogenous glucose production by the liver. Meal-induced insulin secretion is stimulated by (i) rising plasma levels of glucose and other nutrients; (ii) release of incretin peptides, such as glucagon-like peptide 1 (GLP-1), from the gastrointestinal tract; and (iii) adjustments of autonomic tone to pancreatic islets. In addition to coordinating the timing and magnitude of the insulin secretory response [3], the brain can also activate insulin-independent mechanisms that lower blood glucose levels, including both suppression of endogenous glucose production and increase in hepatic glucose uptake (Figure 10.2) [4]. These dynamic interactions illustrate how cooperation between brain, pancreas, liver, and other tissues limits plasma glucose excursion in the post-prandial state. Equally important to glucose homeostasis is maintenance of stable glycaemia in the basal state (i.e. in the absence of ingested nutrients). Unlike the response to a meal, however, insulin-independent mechanisms predominate in the control of glucose disposal in the basal state (i.e. in the absence of nutrient entry from the gastrointestinal tract).

Autonomic control of pancreatic islet function

Brain–islet connections involving both the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) (Figure 10.2) [5] can rapidly influence both insulin and glucagon secretion in response to changes in the level of circulating nutrients and other stimuli under physiological conditions [6].

Recent 3D imaging of cleared human pancreatic islets shows dense innervation by both SNS and PNS fibres [7] and, whereas insulin secretion during a meal is augmented by an associated increase of PNS outflow [3], glucagon section during hypoglycaemia is enhanced by both PNS and SNS outflow to the islet (Figure 10.2) [8]. The liver is also richly supplied with SNS fibres, activation of which stimulates hepatic glucose production, thereby helping to restore normoglycaemia; these fibres are also activated in response to hypoglycaemia [9]. This increased hepatic glucose production is facilitated by increased SNS outflow to pancreatic islets, which potently inhibits insulin secretion in addition to enhancing glucagon release.

The brain also participates in control of islet function under more physiological conditions. For example, the *cephalic phase* of insulin release involves insulin secretion induced by increased PNS outflow to the pancreas that is triggered by feeding cues *before* feeding begins and blood glucose levels begin to rise (Figure 10.2) [10]. This response is mediated primarily by vagal cholinergic signals, is malleable to changing environmental stimuli, and is a large contributor to whole-body glucose tolerance following a meal [11]. Complementing this response is augmented post-prandial insulin secretion resulting from a meal-induced increase of PNS tone.

Autonomic mechanisms also control post-prandial glucagon secretion [12], with local glucagon release in the islet enhancing the responsiveness of insulin-secreting β cells to glucose [13]. These islet responses are likely coordinated by specific glucoregulatory neuronal populations within the hindbrain, midbrain, and hypothalamus that project via multisynaptic relays into the

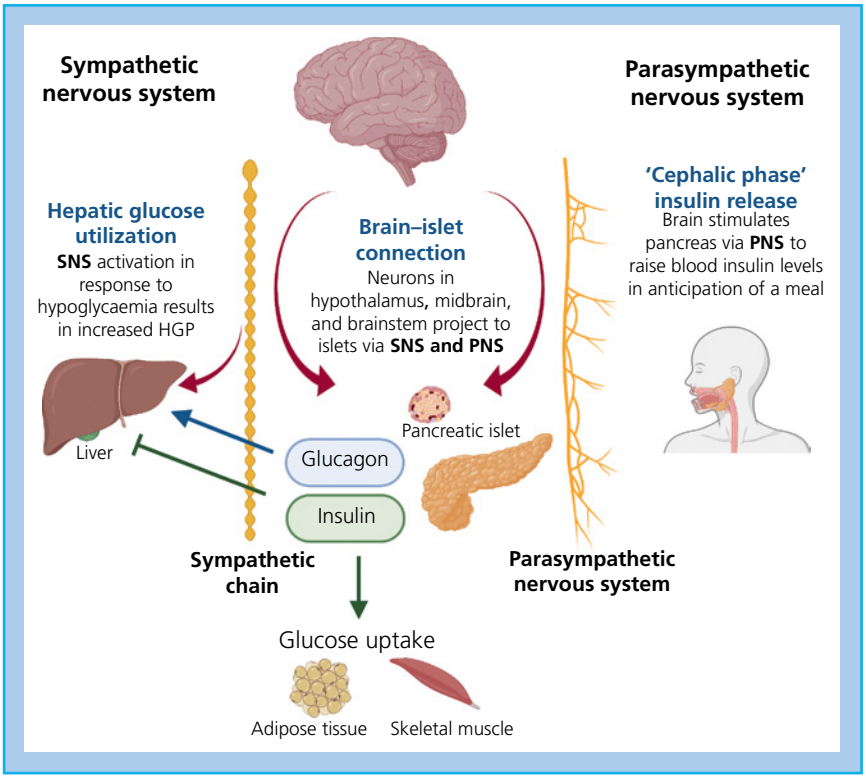

Figure 10.2 Autonomic control of glucose homeostasis. Pancreatic islets receive autonomic input originating with neurons in the hypothalamus, midbrain, and brainstem nuclei that in turn regulate the parasympathetic (PNS) and sympathetic (SNS) nervous system outflow. Glucagon secretion is increased by activation of either PNS or SNS, whereas insulin secretion is stimulated by the former and inhibited by the latter. Sympathetic fibres supplying the liver also affect both hepatic glucose production (HGP) and uptake. In response to hypoglycaemia, therefore, activation of SNS outflow to the liver and pancreas increases both glucagon secretion and HGP, whereas insulin secretion is inhibited. Conversely, insulin release in response to both food consumption and the mere anticipation of a meal is stimulated by activation of PNS supply to pancreatic islets. Source: Figure generated using http://Biorender.com.

pancreas [14–17]. Experimental impairment of neuronal glucose sensing within the mediobasal hypothalamus produces distinct effects on glucose homeostasis through these brain–islet multisynaptic relays [14], which further implicates autonomic input to the islet in its response to both feeding and hypoglycaemia. Although the liver is a major target for the actions of both insulin and glucagon (which suppress and increase hepatic glucose output, respectively), the brain also regulates glucose handling by the liver not only during hypoglycaemia [9], but in response to sustained hyperglycaemia as well. Specifically, both human and rodent studies suggest that intact brain K_{ATP} channel activity is required for the effect of clamped hyperglycaemia to suppress hepatic glucose production [4].

Circadian control of metabolism

The suprachiasmatic nucleus (referred to as the *master circadian pacemaker*) contains neurons whose activity is governed by a system of *clock* genes that is entrained to the light–dark cycle to turn on and off in a circadian manner. This repeating pattern of suprachiasmatic nucleus neuron activation in turn aligns many behaviours and metabolic functions to the circadian clock. For example, hepatic insulin sensitivity (i.e. responsiveness to insulin-mediated suppression of hepatic glucose output) decreases during sleep and increases on waking, in anticipation of the onset of feeding [18, 19], and a specific subset of neurons producing γ-aminobutyric acid (GABA) in the suprachiasmatic nucleus whose rhythmic firing underlies circadian variation in hepatic insulin sensitivity was recently identified [20]. Since normal glucose tolerance depends on proper coupling of insulin secretion to insulin sensitivity, and since mechanisms underlying this coupling remain to be established, it will be interesting to determine if the brain also governs adaptive β-cell response to daily variation in insulin sensitivity. Such a finding would extend previous work linking the brain to adaptive changes of both insulin secretion and insulin sensitivity during cold exposure (discussed later).

How does the brain sense physiological changes in blood glucose?

Although it makes teleological sense for the brain to sense circulating glucose levels (analogous to the recently discovered *Drosophila* glucose-sensing neuron pair, Figure 10.1), precisely how this process occurs remains uncertain. The balance of available literature points to a distributed network of neurons that convey afferent information to the brain regarding both glucose availability and need. Although this brain glucose sensing process can, in theory, involve *glucose-responsive* neurons (or glia) in brain parenchyma [21–24], many of these neurons are exposed only to glucose levels in brain interstitial fluid and not to levels in the circulation. Reliance on glucose sensing by cells exposed only to brain interstitial fluid is unlikely to explain all the effects observed *in vivo*, given that the glucose level in brain interstitial fluid is much lower than in plasma, and that following a change in the plasma level, changes in brain interstitial fluid occur relatively slowly. For these reasons, information regarding the blood glucose level is likely communicated to the brain via a distributed system of neurons (and perhaps glial cells) that are anatomically well placed to sense the circulating glucose level. These include neurons

ALGrawany

located in the vasculature (including the hepatic portal vein, where they are well placed to detect glucose absorbed from the gastrointestinal tract), the gastrointestinal tract itself, and brain areas known as circumventricular organs that are characterized by an incompletely developed blood–brain barrier. Particularly relevant among the latter are the median eminence of the hypothalamus and area postrema of the hindbrain; neurons in these brain areas that are exposed to the circulation may provide the brain with the real-time afferent information needed to mount adaptive responses important for normal glucose homeostasis [25–28].

What, then, might be the primary role in whole-body glucose homeostasis played by cells that sense glucose locally in brain interstitial fluid? While the answer is unknown, many of these parenchymal cells are located within glucoregulatory neurocircuits downstream of peripheral glucose sensors that respond to changes of glycaemia, in addition to detecting changes in brain interstitial fluid glucose levels directly. It is possible, for example, that brain interstitial fluid glucose levels offer a baseline against which afferent information relevant to the circulating level conveyed from peripheral sources can be compared. Additional study is required to clarify the roles of direct and indirect brain glucose-sensing mechanisms in glucose homeostasis; both may in fact contribute, as these possibilities are not mutually exclusive.

Glucose sensing and brain control of energy balance

In addition to multiple hypothalamic nuclei, the bed nucleus of the stria terminalis in the forebrain, and the dorsal vagal complex (comprising the dorsal motor nucleus of the vagus nerve, area postrema, and nucleus of the solitary tract) of the hindbrain are implicated in central regulation of glucose homeostasis [29,30]. Within the hypothalamus, glucose-sensing neurons with intrinsic glucose-responsive characteristics are concentrated in ventromedial, arcuate, and paraventricular nuclei, as well as the lateral hypothalamic area and dorsomedial hypothalamic nucleus (Figure 10.3) [31]. Glucose-responsive neurons can be broadly classified as either glucose excited (analogous to pancreatic β cells) or glucose inhibited [32], and are capable of responding to changes in glucose concentrations (e.g. 1–5 mmol/l) that associate with daily fluctuations in brain interstitial fluid glucose homeostasis [33]. What is less clear is the extent to which the activity of these neurons is regulated by physiological variation in brain interstitial fluid glucose. An alternative possibility is that these intrinsic glucose-sensing properties serve as a marker of neurons involved in glucoregulatory neurocircuits, in the same way that many hypothalamic neurons involved in thermoregulation are marked by intrinsic thermosensory properties [34], even though they do not participate in temperature sensing under physiological conditions. Additional studies are warranted to sort through these possibilities.

Many defined neuronal subtypes involved in energy and glucose homeostasis have these glucose-sensing properties. The melanocortin system, for example, comprises two arcuate neuronal subsets – proopiomelanocortin (POMC) and agouti-related protein (AGRP) neurons – that mediate opposing effects on downstream neuronal targets that express the melanocortin 4 receptor (MC4R) (Figure 10.3) [35]. Thus, whereas POMC neuron activation induces synaptic release of α-melanocyte-stimulating hormone (αMSH), an MC4R agonist, AGRP is an inverse agonist of MC4R that reduces signalling by this receptor. AGRP neurons also regulate feeding behaviour via release of both neuropeptide Y (NPY) and GABA. AGRP and POMC neurons project to a variety of hypothalamic and extrahypothalamic neurons that express MC4Rs; in the paraventricular nucleus, increased melanocortin signalling reduces food intake while reduced melanocortin signalling (resulting from reduced POMC neuron activity, increased AGRP neuron activity, or both) has the opposite effect [36].

Among many observations that establish the key role played by melanocortin signalling in energy and glucose homeostasis is the phenotype induced by genetically impaired melanocortin signalling. Mutations of MC4R, for example, are among the commonest causes of monogenic obesity in humans [37], and variation at the MC4R gene locus associates with human type 2 diabetes in genome-wide association studies [38]. These phenotypes offer direct evidence of the requirement for intact melanocortin signalling for normal energy and glucose homeostasis.

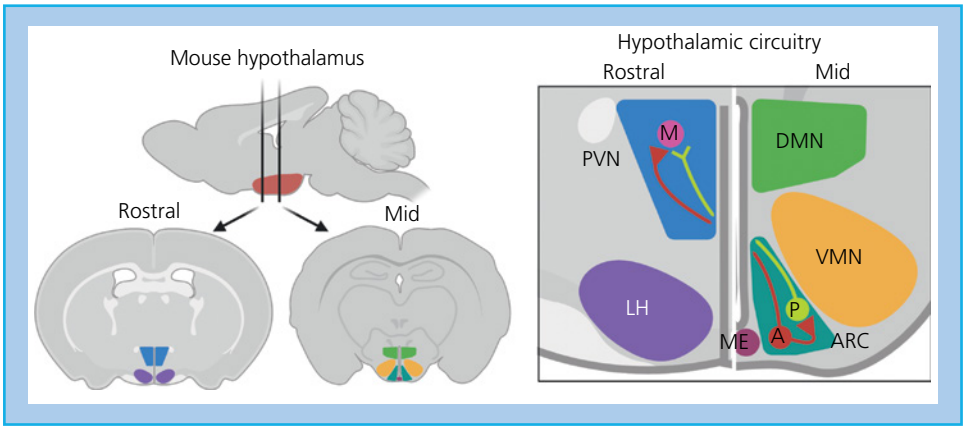

Figure 10.3 Hypothalamic glucoregulatory neurocircuitry implicated in blood glucose control by the brain. Neurons situated in subnuclei spanning the rostral (PVN, paraventricular nucleus; LH, lateral hypothalamic area) and medial (DMN, dorsomedial hypothalamic nucleus; VMN, ventromedial nucleus; ARC, arcuate nucleus; ME, median eminence) hypothalamus are implicated in central control of glucose homeostasis. Melanocortin 4 receptor signalling (M) in neurons in the PVN and elsewhere is stimulated by the agonist α-MSH released by proopiomelanocortin (P, light green) neurons, and inhibited by the inverse agonist agouti-related peptide (A) released by AGRP neurons (A, red) located in the medial ARC region of the mediobasal hypothalamus. AGRP neurons also synapse onto and inhibit proopiomelanocortin (POMC) neurons, and both POMC and AGRP neurons project into the ME, which lacks a fully formed blood–brain barrier, thus allowing subsets of these neurons to sense the circulating glucose level. Source: Figure generated using http://Biorender.com.

Importantly, melanocortin signalling is highly responsive to nutritional state owing to coordinated, reciprocal regulation of AGRP and POMC neuron activity by afferent input from leptin and other relevant humoral signals. In response to fasting or other conditions associated with depletion of body fuel stores, for example, AGRP neurons are activated whereas POMC neurons are inhibited, a combination that potently reduces melanocortin signalling and promotes increased food intake, reduced energy expenditure, and recovery of lost weight [39]. These reciprocal neuronal responses are elicited by the effect of fuel depletion to lower circulating levels of leptin, insulin, and glucose, and to increase secretion of the gastric hormone ghrelin [39]. Although some POMC and AGRP neurons qualify as either glucose excited or inhibited [40], the extent to which these intrinsic glucose-sensing properties drive *in vivo* responses is unclear.

Another hypothalamic area involved in glucose energy homeostasis is the ventromedial nucleus. Subsets of these neurons constitute a key node in the circuit responsible for mounting counter-regulatory responses to hypoglycaemia. Unexpectedly, a specific subset of these neurons is also implicated in the pathogenesis of hyperglycaemia in diabetic mice. Many ventromedial nucleus neurons are also glucose responsive [40], but once again, the extent to which the activity of these neurons is determined by intrinsic glucose sensing *in vivo* (as opposed to afferent input from other neurons in a circuit) awaits further study.

In addition to neurons, many glial cell types are implicated in brain regulation of glucose homeostasis (Figure 10.4). Astrocytes are the commonest glial cell type in the brain, and direct connections (via gap junctions) exist between these cells and both neurons and other glial cells [41]. Interestingly, gap junction subunits (connexins 30 and 43) expressed by hypothalamic astrocytes appear to be critical for brain glucose sensing and control of insulin secretion during a glucose challenge [42]. This may reflect the fact that astrocytes are essential components of the blood–brain barrier, and are implicated in glucose transport into the brain (via glucose transporter 1 (GLUT1) and possibly GLUT2) [43]. Glucose taken up into astrocytes can be metabolized into lactate, which can then be released as a source of fuel for neurons in a process known as the astrocyte–neuron lactate shuttle (Box 10.1) [41,44]. Additionally, astrocytes express insulin receptors, deletion of which reduces the responsiveness of POMC neurons to elevated glucose levels [45].

Tanycytes are another glial cell type implicated in central nervous system (CNS) glucose sensing (Figure 10.4). Tanycyte cell bodies line the surface of the third cerebral ventricle, and from there they extend filamentous processes deep into medial hypothalamic structures including the arcuate, ventromedial, and dorsomedial nuclei and median eminence. One proposed role for these cells is to sense and/or transport glucose from the cerebrospinal fluid to these parenchymal areas [31,46], but the extent to which tanycytes participate in this type of glucose sensing is unclear. One group found that treatment with alloxan to ablate tanycyte glucose sensing strongly interfered with both counter-regulatory responses to hyperglycaemia and responses to hyperglycaemia [47], while another group reported that conditional tanycyte ablation predisposes to obesity and elevated fat mass, but with little effect on glycaemia [48].

Another noteworthy aspect of hypothalamic glial cells in relation to metabolic diseases pertains to their response to consumption of an obesogenic diet [49]. Rodent studies demonstrate that following the switch to a high-fat diet, *reactive gliosis* (characterized by inflammatory activation of both astrocytes and microglia) occurs

Box 10.1 Astrocyte–neuron glucose lactate shuttle hypothesis

Glucose transported across the blood–brain barrier by astrocytes is metabolized into lactate, which in turn is made available to neurons and is hypothesized to serve as both a fuel source for neurons and a mechanism for sensing the peripheral glucose levels [41,44,78]. Evidence in favour of the latter theory is as follows:

- Glucose-excited neurons in the hypothalamus are activated by lactate as well as glucose [79].
- These neurons express monocarboxylate transporters (MCTs), which facilitate lactate transport [80].
- Neuronal lactate sensing is implicated in peripheral lipid metabolism [81] and experimental induction of lactate dehydrogenase (responsible for metabolizing glucose to lactate) in the hypothalamus is sufficient to lower blood glucose in obese rodents [82].

However, the extent to which brain neurons depend on lactate vs. glucose as a fuel is uncertain. Inhibition of glucokinase (a key rate-limiting step for glucose oxidation in these neurons) lowers activity of glucose-excited and increases activity of glucose-inhibited neurons [83,84] implying that they are sensing glucose, rather than lactate. Additional research into the role of astrocyte lactate production in brain glucose sensing is a priority.

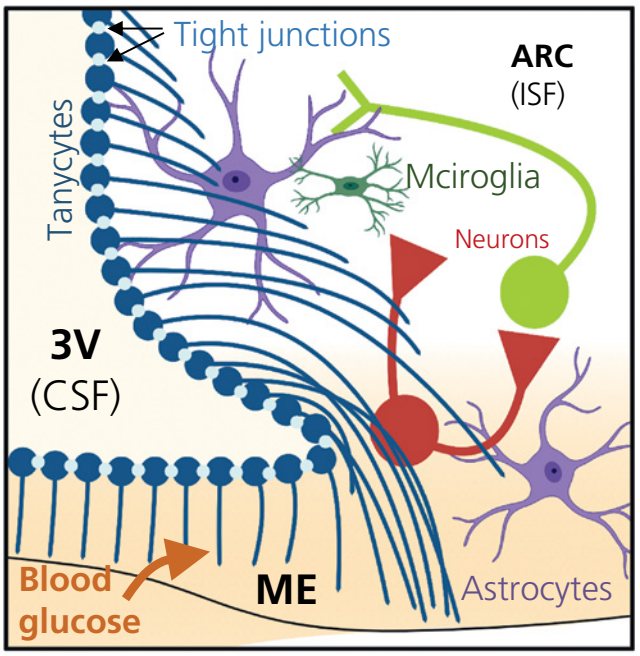

Figure 10.4 Glucose-sensing cells in the mediobasal hypothalamus. The median eminence (ME) is a circumventricular organ situated at the floor of the mediobasal hypothalamus (MBH) that lacks a fully formed blood–brain barrier. Since the ME is bordered dorsally by the third cerebral ventricle (3V), neurons and glial cell types in this brain area and adjacent arcuate nucleus (ARC) have access to glucose in the bloodstream, in cerebrospinal fluid (CSF) and in brain interstitial fluid (ISF). Cell types capable of sensing glucose include neurons (red and green), astrocytes (purple), and tanycytes (blue). Obesity-associated hypothalamic gliosis is characterized by inflammatory activation of astrocytes (purple) and microglia (green) and is hypothesized to impair both energy and glucose homeostasis, potentially by adversely affecting glucose sensing by cells in this brain area. Source: Figure generated using http://Biorender.com.

rapidly (within days) in the mediobasal hypothalamus, and that weight gain induced by this diet is limited when this activation response is blocked [50, 51]. Thus, reactive gliosis appears to be required for the full expression of diet-induced obesity in mice. This pathological response is also present in humans with obesity and associates with insulin resistance, even after adjustment for differences of body weight [52]. Microglial mitochondrial dynamics are reportedly involved in this gliosis response; in mice with diet-induced obesity [53], abnormal POMC neuron responses to hyperglycaemia depend on these microglial changes. Establishing the contribution made by reactive mediobasal hypothalamus gliosis to the pathogenesis of human obesity and type 2 diabetes is an important scientific priority.

Glucose transporters and brain glucose uptake

Members of the GLUT family vary widely with respect to affinity for glucose, transport capacity, tissue distribution, and physiological function. There are 14 known GLUT family members, with one or more being expressed in almost every cell type to facilitate cellular glucose uptake [54]. Table 10.1 summarizes the characteristics of the different GLUT family members.

GLUT1 is a high-affinity, low-capacity glucose transporter, which means that its glucose transport capacity is saturated at concentrations below those usually maintained in the circulation. Consequently, a rise in the plasma glucose level is not typically associated with a proportionate increase in cellular glucose uptake via this transporter. GLUT1 is widely expressed throughout the body, including by endothelial cells and astrocyte processes that form the blood–brain barrier, and is a major transporter for delivery of glucose into the brain [55]. GLUT1 expression in the blood–brain barrier is upregulated under conditions such as hypoxia and hypoglycaemia where neuronal adenosine triphosphate (ATP) generation is compromised as a means to enhance glucose transfer into the brain [56]. Such findings are consistent with glucose transport across the blood–brain barrier by GLUT1 constituting the rate-limiting step in brain glucose delivery [54]. Interestingly, obesity is associated with reduced blood–brain barrier expression of GLUT1 in mice [70]; the finding that hyperglycaemia is associated with reduced brain glucose uptake in people with type 2 diabetes also suggests that similar changes occur in the blood–brain barrier of humans with metabolic dysfunction.

GLUT2 is expressed uniquely by cell types specialized for cellular glucose sensing, both in the brain (including glucose-responsive neurons, astrocytes, and tanycytes [71–73]) and in the periphery (pancreatic β cells, intestinal epithelial cells, hepatocytes, and kidney cells) [74]. GLUT2 has a much higher K_m for glucose (17 mM) than other glucose transporters, enabling the rate of cellular glucose transport to vary across the full range of extracellular glucose levels [58]. Consequently, this transporter enables changing circulating glucose levels to elicit a proportionate change in cellular uptake. Most cells that express GLUT2 also express glucokinase, an enzyme that, owing to its similarly high K_m for glucose (compared to other hexokinase isoforms), enables the rate of glucose phosphorylation to vary with the extracellular glucose level in glucose-sensing cells. While GLUT2 levels in the periphery increase during acutely elevated glycaemia, some insulin-resistant conditions are associated with reduced hypothalamic GLUT2 expression [75]. Furthermore, GLUT2 is implicated in the brain's ability to mount counter-regulatory responses to hypoglycaemia [76].

GLUT3 is the predominant GLUT subtype expressed by neurons and is characterized by a lower K_m than other neuronal GLUTs [62], thus enabling efficient neuronal glucose transport from brain interstitial fluid where glucose concentrations are much lower than in the bloodstream [63]. By comparison, GLUT4 is expressed in so-called *insulin-sensitive* tissues (tissues in which insulin binding to its receptor induces glucose uptake, including adipocytes, cardiomyocytes, and skeletal muscle [77]). Translocation of GLUT4 from the cytosol to the plasma membrane in response to insulin is responsible for insulin-stimulated glucose uptake and associated insulin-mediated glucose clearance from the bloodstream. This mechanism plays a key role in promoting glucose disposal following a meal (e.g. when glucose and insulin levels are elevated). In the brain, GLUT4 is expressed in distinct populations, including by forebrain cholinergic neurons that also express GLUT3 [64], but the extent to which this GLUT4 is truly insulin responsive and mediates glucose uptake in these neurons awaits further study.

GLUT8 has a low K_m for glucose, and its role in cellular glucose uptake remains uncertain, since glucose competes with fructose and galactose for transport via this transporter subtype [67]. In the brain, GLUT8 is expressed by neurons of the hypothalamus, cerebellum, brainstem, and hippocampus, where it is located in proximal and distal dendrites [68]. Like GLUT4, this transporter resides primarily in the cytosol and is hypothesized to be translocated to the cell surface in response to stimuli that remain to be identified. The extent to which GLUT8 transports other substrates preferentially over glucose also remains to be determined [69].

Table 10.1 The glucose transporter family.

Glucose transporter	Central cell types	K_m for glucose	Description	References
GLUT1	Endothelial blood–brain barrier, astrocytes	1–2 mM	Implicated as *rate limiting* for glucose transport across the blood–brain barrier	[55–57]
GLUT2	Glucose-sensing neurons, astrocytes, tanycytes	15–20 mM	High-capacity, low-affinity glucose transporter implicated in cellular glucose sensing	[58–61]
GLUT3	Most neurons	1–2 mM	Lower K_m compared to other GLUTs, implicated as primary neuronal glucose transporter	[59, 62, 63]
GLUT4	Mostly peripheral, a subset of cholinergic neurons in the forebrain	5 mM	Insulin-responsive glucose transporter implicated in insulin-mediated glucose disposal	[57, 58, 64–66]
GLUT8	Neurons of hypothalamus, cerebellum, brainstem, hippocampus	2 mM	Hypothesized to function similarly to GLUT4 in response to an as yet unidentified signal	[67–69]

Evidence supporting indirect blood glucose sensing by the brain

A defining feature of a homeostatic control system is that it not only accurately interprets the current state of the biological system, but also utilizes past experiences to condition the system to preemptively respond to and effectively counteract anticipated regulatory challenges [85]. Such an arrangement allows for the control system to engage in a corrective response at even the slightest perturbation of homeostasis, prior to a detectable change in the defended biological measure, thus enabling the biological variable to remain within its homeostatic range.

Parallels to brain control of thermoregulation

Brain control of thermoregulation offers a useful paradigm for understanding control of glucose homeostasis by the CNS. To ensure the stability of core body temperature, changes in ambient temperature are continuously relayed from afferent thermosensory fibres supplying the skin. These neurons project to the spinal cord, where they synapse onto ascending sensory neurons that ultimately supply neurons in the hypothalamic preoptic area (Figure 10.5) [86]. Preoptic area neurons in turn transduce this thermosensory input into adaptive responses that govern both heat production and dissipation (e.g. activation of brown adipose tissue, shivering, cutaneous vasoconstriction) so as to preserve the constancy of the brain's temperature [87].

Homeostasis of body temperature is therefore achieved via a multiorgan process that enables the brain to anticipate the need for adaptive responses before internal body temperature even begins to change. This degree of control would not be possible if the system relied on direct temperature sensing by neurons in the brain (rather than cutaneous sensory innervation), since the brain's temperature would have to change before a homeostatic response would be engaged. Yet many key neurons in the medial preoptic area of the mediobasal hypothalamus that coordinate these responses have intrinsic temperature-sensing properties, analogous to the glucose-sensing properties of neurons involved in brain regulation of glucose homeostasis (Figure 10.5).

Taking this analogy a step further, both 'warm-sensitive' and 'cold-sensitive' neurons have been identified in the hypothalamic preoptic area, just as both 'glucose-excited' and 'glucose-inhibited' neurons populate hypothalamic nuclei involved in glucose homeostasis. Similarly, direct activation of temperature-sensing neurons can powerfully impact thermoregulation, and direct activation of glucose-sensing neurons can powerfully impact glucose homeostasis. Yet under physiological conditions, thermoregulation does not involve changes in brain temperature; instead, this intrinsic

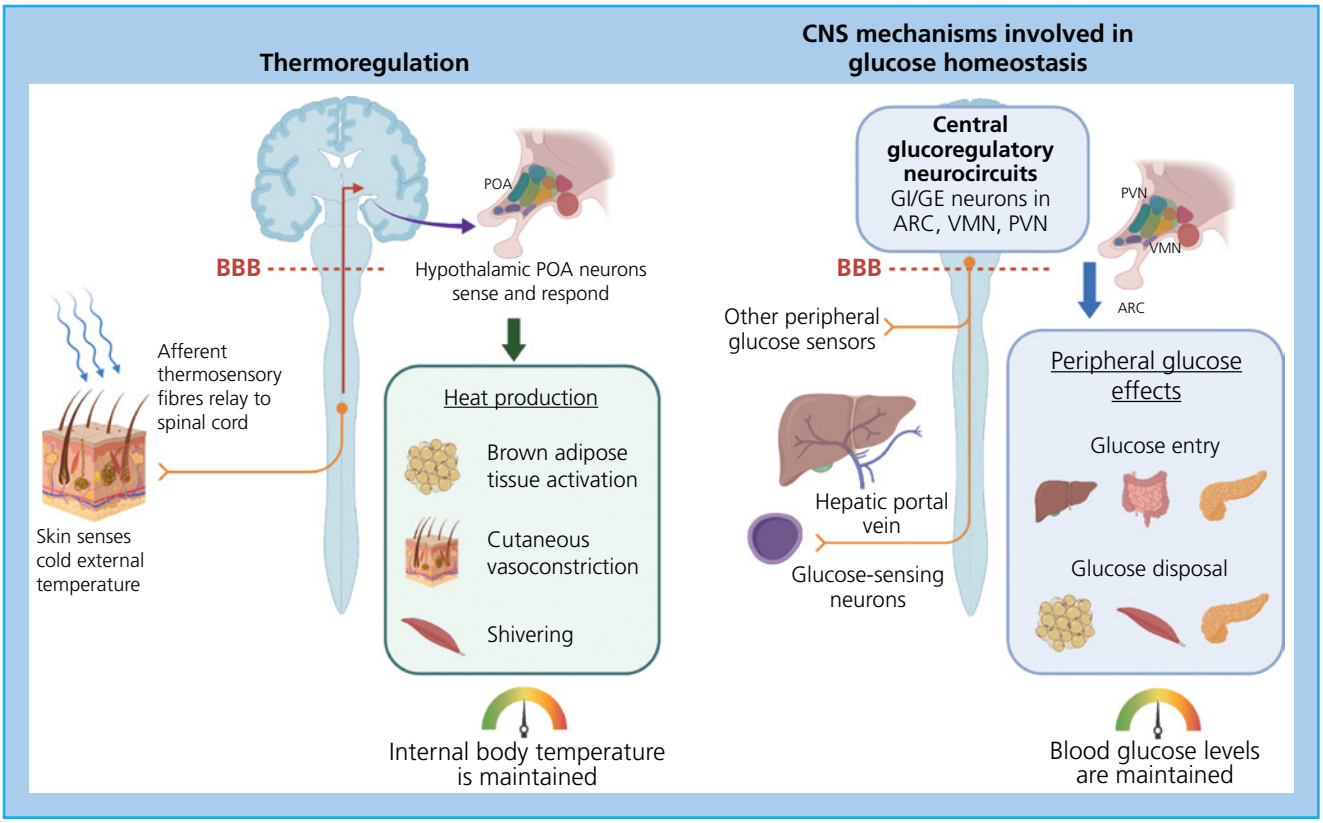

Figure 10.5 Comparison of central thermoregulatory and glucoregulatory systems. The thermoregulatory system senses changes in external temperature via afferent thermosensory fibres supplying the skin, and conveys this information via a multisynaptic pathway to the hypothalamic preoptic area (POA). In this brain area, relevant afferent input is transduced into adaptive changes in heat production and dissipation that effectively maintain internal body temperature within a narrow range. Brain control of whole-body glucose homeostasis is hypothesized to employ an analogous system whereby afferent input regarding the circulating glucose level is conveyed to glucoregulatory neurocircuits in the hypothalamus and elsewhere by glucose-sensing neurons situated both in circumventricular areas of the brain that lack a fully formed blood–brain barrier and in peripheral vasculature (e.g. hepatic portal vein). In partnership with pancreatic islets, centrally driven changes in peripheral glucose production and utilization promote stability of the circulating glucose level. ARC, arcuate nucleus; BBB, blood–brain barrier; CNS, central nervous system; GE, glucose excited; GI, glucose inhibited; PVN, paraventricular nucleus; VMN, ventromedial nucleus. Source: Figure generated using http://Biorender.com.

temperature-sensing capacity may provide a 'back-up' or 'fail-safe' mechanism that becomes important only when brain temperature deviates from its physiological range (owing to extreme environmental exposure or failure of 'first-line' physiological defences). By analogy, direct sensing of glucose by neurons in the brain may be relevant primarily under pathological conditions, with input relevant to physiological control being provided primarily by afferent glucose-sensing neurons innervating the vasculature itself. From this perspective, the capacity to maintain brain glucose levels within a narrow physiological range, even in the face of wildly fluctuating variation in plasma glucose levels [88–90], seems likely to involve afferent input regarding the blood glucose level provided to the brain from the periphery (Figure 10.5).

In support of this type of mechanism, glucose-sensing neurons supply the hepatic portal vein [91] and sense ingested glucose as it enters the circulation from the gastrointestinal tract, prior to entry into systemic circulation. An increase of glucose levels in the hepatic portal vein relative to the systemic circulation constitutes a *portal signal* that is detected by these neurons and implicated as a trigger driving the marked increase of hepatic glucose uptake elicited by a meal. Although the underlying mechanisms have yet to be fully elucidated, this response appears to be mediated via reduced SNS outflow to the liver, which in turn activates liver glucokinase, the rate-limiting enzyme for glucose uptake into hepatocytes [92]. Defects in this response are seen in a canine model of diet-induced obesity [93, 94], and support the hypothesis that reduced hepatic glucose uptake secondary to increased SNS outflow to the liver contributes to glucose intolerance in this setting.

Integration of glucose homeostasis, energy homeostasis, and thermoregulation

In temperate regions, mammals are routinely exposed to ambient temperatures sufficiently low to pose a substantial homeostatic challenge. As the environmental temperature drops, the increase of heat production needed to prevent hypothermia is achieved via increased SNS outflow to thermogenic tissues (primarily skeletal muscle and brown adipose tissue), which generate heat by potently increasing glucose and free fatty acid oxidation [95, 96]. Once in motion, this process creates two additional homeostatic challenges: (i) averting depletion of fuel stores in the face of markedly increased energy expenditure; and (ii) preserving euglycaemia in the face of markedly increased rates of glucose uptake from the circulation.

From this perspective, it seems remarkable that neither body temperature, body fat mass, nor blood glucose levels are detectably altered when mice or rats are moved from a warm to a cool environment, provided they have sufficient access to food. The stability of body temperature is ensured by rapidly increasing heat production in a manner that precisely offsets heat loss, and this effect is associated with (i) an increase of food intake that precisely offsets the increase of energy expenditure; and (ii) an increase of glucose production that precisely offsets the increase of glucose disappearance from plasma. Increased SNS outflow is crucial to these adaptive responses [97], including suppression of glucose-induced insulin secretion, which enables glucose to be mobilized in amounts sufficient to meet the increased demand for tissue glucose utilization. These highly integrated responses highlight how the brain integrates afferent information relevant to a changing external environment with interoceptive signals and humoral cues (e.g. input from leptin and glucose) relevant to changing body fuel requirements, to mount adaptive responses with sufficient precision to protect body temperature while ensuring stability in levels of both stored and circulating fuel (Figure 10.5).

Brain responses to perceived glucose deficiency

The lower boundary of the BDL_G is established primarily by the brain, which mounts counter-regulatory responses that restore low blood glucose levels to their baseline value [98]. The threshold glucose level for activating brain-driven components of the counter-regulatory responses, such as secretion of adrenaline (epinephrine) and activation of SNS outflow to liver and pancreas, serves as a biomarker for what the brain perceives as the lower limit of the physiological range of blood glucose. However, because this lower boundary is seldom crossed in healthy individuals, the brain's role in the counter-regulatory response is usually viewed as an emergency response to a severe pathological state rather than a fundamental aspect of everyday glycaemic regulation.

The brain's role in defending the lower boundary of the BDL_G can be investigated using experimental *neuroglycopaenia*. This term describes the state induced by reducing glucose availability to the brain through administration of a non-metabolizable glucose analogue (e.g. 2-deoxyglucose [99], which is taken up by cellular glucose transporters and phosphorylated by glucokinase or other hexokinases, but cannot be further metabolized) that impairs neuronal glucose utilization. In response to neuroglycopaenia, the brain mounts counter-regulatory responses that mimic those induced by hypoglycaemia. Sympathetic outflow to the pancreas also increases, which inhibits insulin secretion while enhancing glucagon secretion [6, 100]; this glucagon response is impaired by sympathetic denervation of the pancreas [101].

These counter-regulatory responses serve collectively to increase glucose production while decreasing peripheral glucose utilization and, unlike the response to hypoglycaemia, which serves to restore low blood glucose back to normal, the brain response to neuroglycopaenia causes blood glucose concentrations to rapidly rise out of the normal range. Intriguingly, so long as the brain perceives an insufficient supply of glucose, it will actively maintain this hyperglycaemic plateau, with blood glucose levels returning to baseline only after the drug effect has worn off [99]. Thus, the brain responds to the perception of reduced glucose availability by inducing and maintaining hyperglycaemia so as to deliver sufficient glucose to the brain to overcome the underlying defect. This hyperglycaemic response can be fully recapitulated in mice by experimental activation of ventromedial nucleus neurons in glucoregulatory neurocircuits responsible for mounting counter-regulatory responses [21, 102, 103].

Hypothesis: reduced brain glucose sensing predisposes to hyperglycaemia in type 2 diabetes

The brain's ability to raise the defended blood glucose level during neuroglycopaenia raises the question of whether a similar mechanism – perception of reduced glucose availability by the brain – might contribute to hyperglycaemia in people with type 2 diabetes. This hypothesis fits with evidence that the defended lower limit of blood glucose is ~40% higher in people with type 2 diabetes than in those without (based on the blood glucose threshold for counter-regulatory response activation) [104, 105]. A similar situation applies to individuals with monogenic diabetes caused by glucokinase mutations [106]. Because glucose sensing is reduced, the

brain can be expected to perceive circulating glucose levels to be lower than they truly are, with the consequence being an increase in the defended blood glucose level, as occurs in response to neuroglycopaenia. Consistent with this prediction, these individuals are characterized by generally normal glucose homeostasis, except that (i) the BDL_G is elevated compared to normal individuals [104]; and (ii) the threshold for activating CNS-driven counter-regulatory responses during hypoglycaemia (e.g. epinephrine secretion) is increased, mimicking what is observed in type 2 diabetes [104, 105].

Although glucokinase mutations impair glucose sensing in both pancreatic β cells and neurons, the upward resetting of the glycaemic threshold for epinephrine secretion can only be explained by CNS involvement, since β-cell glucose sensing plays no role in adrenomedullary axis regulation. The elevated glycaemic threshold for epinephrine secretion in individuals with glucokinase mutations therefore offers *prima facie* evidence that impaired neuronal glucose sensing is sufficient to raise the lower boundary of the defended BDL_G in humans, thus raising the possibility of a similar situation in people with type 2 diabetes. Stated differently, these findings suggest that a primary defect in brain glucose sensing and associated elevation of the BDL_G may contribute to the pathogenesis of type 2 diabetes.

Evidence derived from investigation into the role of ventromedial nucleus neurons in glucose homeostasis and diabetes pathogenesis in mouse models strengthens the hypothesis. Specifically, silencing a specific subset of neurons located in the circuit responsible for mounting counter-regulatory responses located in the hypothalamic ventromedial nucleus not only blunts the counter-regulatory response to neuroglycopaenia, but also causes a 25% reduction in the circulating glucose level in otherwise normal mice [103]. These neurons, which are marked by expression of the cholecystokinin B (CCKB) receptor subtype, therefore help to establish the BDL_G in mice. More importantly, when mice become diabetic by destruction of pancreatic β cells, silencing of these neurons potently ameliorates hyperglycaemia [103]. Activation of this ventromedial nucleus neuronal subset therefore appears to be required for hyperglycaemia induced by severe insulin deficiency. This in turn raises the possibility that an impaired capacity of the brain to sense blood glucose levels leads to activation of ventromedial nucleus neurons involved in glucose counter-regulation, analogous to the response to neuroglycopaenia; in response this perceived glucose deficiency, neurocircuits are activated that raise the BDL_G. This model does not dismiss or exclude key roles for insulin resistance or impaired β-cell function in the pathogenesis of type 2 diabetes; on the contrary, brain responsiveness to rising blood glucose levels may decline in parallel with peripheral metabolic impairments, possibly involving shared underlying mechanisms (e.g. systemic and hypothalamic inflammation).

The transition from obesity to type 2 diabetes

Obesity and type 2 diabetes are closely related metabolic disorders – not only in their tendency to affect the same individuals, but in their underlying pathogenic processes. Analogous to the gradually rising BDL_G characteristic of type 2 diabetes, obesity can be defined as a state in which excessive weight gain and body fat mass remain biologically defended as they increase outside of the normal range [107]. One hypothesis to explain this defended elevation of body fat mass is that the brain becomes *resistant* to input from adiposity-related negative feedback signals (e.g. leptin) that inform the brain regarding the status of body fuel stores [107, 108]. So long as the brain perceives the amount of body fat to be lower than it actually is, it will activate responses that promote a positive energy balance until body fat mass increases sufficiently to overcome the resistance. The net effect is an increase in the biologically defended level of body fat mass that raises circulating negative feedback signals sufficiently to overcome the brain's resistance to this input. A point to emphasize is that this mechanism is advanced to explain not how weight gain occurs, but rather how body fat stores continue to be defended even as they rise out of the normal range.

The hypothesis that the pathogenesis of type 2 diabetes involves a progressive impairment in the brain's ability to sense glucose availability, thus raising the BDL_G to a level sufficient to overcome the underlying defect, offers a feasible explanation for the transient nature of glucose lowering induced by anti-diabetes drugs currently in use (e.g. metformin, sulfonylureas, or insulin) since, once the drug effect has worn off, the blood glucose level returns to its biologically defended value. From this perspective, the increased BDL_G in type 2 diabetes is hypothesized to result as a compensatory response to an intrinsic impairment in brain sensing of the circulating glucose level (or a defective response to this input) [109]. Indeed, defects in brain glucose responsiveness and transport are both well documented in humans with type 2 diabetes [110–112].

The hypothesis that obesity and type 2 diabetes involve biologically defended elevations of body fat mass and blood glucose level, respectively, and that these responses are mounted by the brain to compensate for impaired sensing of relevant feedback signals, begs the question of whether a shared defect might be at work. While this possibility is speculative at present, the extensive overlap in hypothalamic neurocircuitry involved in the regulation of stored fuel (i.e. body fat mass) and circulating fuel (i.e. glucose) is compatible with this idea. Future research should determine whether the close association between obesity and type 2 diabetes stems in part from a shared defect in sensing of afferent input by brain systems involved in both energy and glucose homeostasis [77, 113].

Roles of insulin-dependent and -independent glucose lowering by the brain

Although glucose lowering in the post-prandial state is mediated predominantly by insulin-dependent mechanisms, glucose disposal in the fasting state is largely insulin independent [114, 115]. It therefore follows that impairment of either mechanism of glucose disposal could contribute to the elevated basal glucose level characteristic of type 2 diabetes.

Glucose effectiveness is a term used to describe the ability of a rise in the plasma glucose level to promote its own disposal independently of insulin, and it provides a useful measure of insulin-independent glucose lowering. Evidence linking reduced glucose effectiveness to the pathogenesis of type 2 diabetes was first provided by Welch et al. [116], who showed that in individuals with type 2 diabetes, not only is insulin sensitivity reduced as expected, but glucose effectiveness is also reduced by ~40%. A follow-up study showed that among 18 lean and obese individuals without diabetes, those with impaired glucose tolerance not only had the expected lowering of insulin-dependent glucose disposal, but also twofold lower glucose effectiveness [117]. Glucose intolerance in individuals without diabetes, therefore, appears to involve impairment of both insulin-dependent and -independent mechanisms.

To investigate the contributions of these impairments to the development of type 2 diabetes, a prospective cohort study was conducted in 181 normoglycemic individuals at high risk of type 2 diabetes (offspring of parents who both had type 2 diabetes) [118]. Over a 20-year follow-up period, 16% of these individuals developed type 2 diabetes, and among these at-risk individuals, reductions of both glucose effectiveness and insulin sensitivity were detectable at

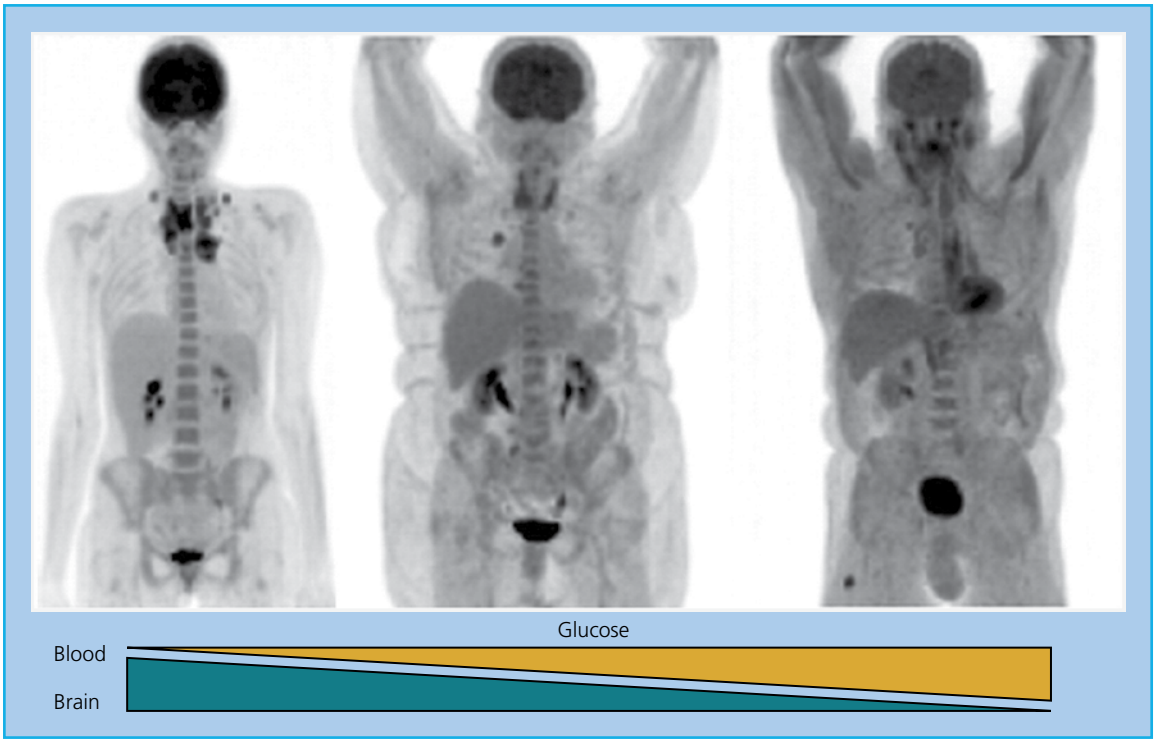

Figure 10.6 Diabetes reduces glucose uptake from blood into brain. 90 individuals were fasted for 6–8 hours before deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG) intravenous administration and positron emission tomography (PET) imaging. The maximum standardized uptake value (SUV_{max}) for cerebral/brain ^{18}F-FDG uptake was decreased in association with increased serum glucose (BGL): BGL <80 mg/dl, SUV_{max} 15.9 ± 5.4; BGL 80–100 mg/dl, SUV_{max} 14.5 ± 3.7; BGL 100–120 mg/dl, SUV_{max} 12.5 ± 3.5; BGL 120–140 mg/dl, SUV_{max} 12.3 ± 3.09; BGL 140–160 mg/dl, SUV_{max} 9.8 ± 2.6; BGL 160–180 mg/dl, SUV_{max} 8.2 ± 1.9; BGL >180 mg/dl, SUV_{max} 8.6 ± 4.7. Representative images of ^{18}F-FDG PET/CT brain glucose uptake in individuals with low (left, BGL 65 mg/dl, no diabetes, no insulin), mid (middle, BGL 155 mg/dl, no diabetes, no insulin), and high (right, BGL 298 mg/dl, no diabetes, after insulin) blood glucose levels. Darker regions represent more sugar utilization and tracer accumulation. Source: From Büsing et al. 2013 [122].

least 10 years prior to diagnosis, with reduced glucose effectiveness conferring the greatest relative risk [118]. These findings clearly implicate impairment of insulin-independent glucose disposal, along with impaired insulin secretion and insulin sensitivity, in the pathogenesis of type 2 diabetes.

Given the large literature implicating β-cell dysfunction in type 2 diabetes, it seems paradoxical that hyperinsulinaemia was recently reported to be predictive of future type 2 diabetes development [119–121]. A key unanswered question is the mechanism underlying this hyperinsulinaemia. Given that this phenotype was reported in individuals with normal glucose tolerance and normal insulin sensitivity [119], and since the combination of hyperinsulinaemia and normal insulin sensitivity should result in improved glucose tolerance unless glucose effectiveness is also reduced, the possibility that hyperinsulinaemia is a biomarker of reduced glucose effectiveness is consistent with evidence linking reduced glucose effectiveness to the future development of type 2 diabetes in humans [118]. Future studies should address two key questions: (i) is hyperinsulinaemia a biomarker of reduced glucose effectiveness in individuals at risk for type 2 diabetes? And (ii) given the brain's ability to regulate glucose effectiveness, does a brain defect contribute to the mechanism underlying reduced glucose effectiveness (and hyperinsulinaemia) in the pathogenesis of type 2 diabetes?

Clinical evidence supporting altered brain blood glucose handling in individuals with diabetes

A clinical study using magnetic resonance spectroscopy (MRS, which can be used to measure relative changes of brain glucose content over time in humans) reported that compared to healthy individuals, those with obesity have reduced brain glucose uptake during a hyperglycaemic clamp, and that this defect is even more pronounced in individuals with suboptimally managed type 2 diabetes [110]. Similar results have been generated using positron emission tomography (PET) imaging, which can measure glucose uptake into brain or other tissues (using a positron-labelled glucose analogue). One PET imaging study of a large cohort of individuals with or without type 2 diabetes showed that higher blood glucose levels are associated with lower brain glucose uptake (Figure 10.6) [112, 122], and that the brain is the only organ in which glucose uptake was related to glycaemia [112]. Although more work is needed, these brain imaging findings support the hypothesis that the brain's ability to sense and respond to changes in glycaemia is impaired in type 2 diabetes.

Targeting the brain to restore normoglycaemia

Brain-directed treatments have been identified over the past decade that can return elevated plasma glucose levels to the normal range in rodent models of both type 1 diabetes and type 2 diabetes. For the most part, these interventions (i) target the mediobasal hypothalamus; (ii) rely primarily on insulin-independent glucose-lowering mechanisms; and (iii) reset the BDL_G to normal, rather than simply lowering glucose levels in a transient manner.

Several members of the fibroblast growth factor (FGF) family of peptides elicit potent glucose-lowering actions in rat and mouse models of type 2 diabetes following central administration.

Initially, studies focused on two hormones in this family, FGF-21 and FGF-19, which are secreted primarily from the liver and intestine, respectively [123]. Although each has distinct physiological functions, pharmacological administration of either peptide can normalize blood glucose levels in multiple rodent models of type 2 diabetes [124]. Although these effects were originally proposed to be mediated via peripheral mechanisms, they were subsequently shown to be mediated primarily in the brain [124, 125].

Meanwhile, the growth factor FGF-1 elicits a more a durable anti-diabetes action. Like FGF-19 and FGF-21, this effect was first reported following systemic administration [126], but was subsequently found to be highly effective following intracerebroventricular FGF-1 injection at a dose too low to have systemic effects. What distinguishes FGF-1 from any other pharmaceutical treatments of type 2 diabetes, however, is that a single intracerebroventricular injection can normalize glycaemia for weeks to even months in rodent models of type 2 diabetes, despite having no sustained effect on food intake, body weight, or body adiposity (Figure 10.7) [127]. Cellular mechanisms underlying the hypothalamic response to FGF-1 appear to involve glia–neuron interactions [128] that increase melanocortin signaling and are accompanied by reversal of maladaptive changes in the extracellular matrix [128, 129]. Whether these findings will translate to more effective treatment strategies for human type 2 diabetes awaits additional study. A key final point related to central actions of FGF1 (as well as leptin) in diabetic animals is that beyond simply lowering elevated plasma glucose levels, *these interventions appear to restore the* BDL_G *to normal.*

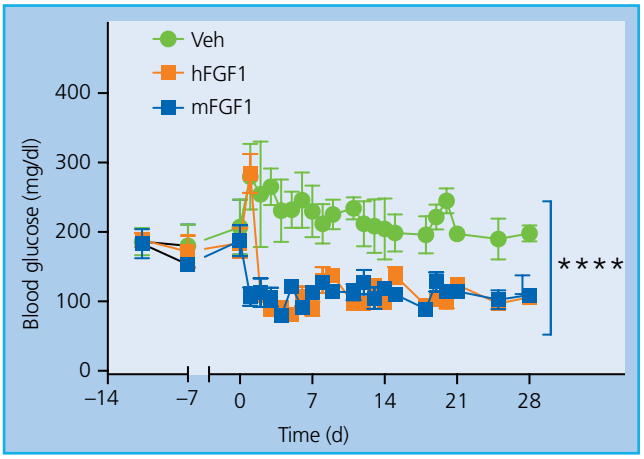

Figure 10.7 Sustained blood glucose lowering by central fibroblast growth factor (FGF)-1 treatment in a mouse model of type 2 diabetes. A single intracerebroventricular injection of human (hFGF1) or mouse (mFGF1) at a dose of 3 μg induces sustained diabetes remission in diabetic $Lep^{ob/ob}$ mice. Source: Adapted with permission from Morton et al. 2015 [125].

Current and future anti-diabetes drugs that target central pathways

Anti-diabetes agents in current use can act on tissues ranging from the pancreas to muscle, adipose tissue, liver, kidney, and gut, with some also acting in the brain (Table 10.2). Perhaps the most clear-cut example of the latter is the dopamine agonist bromocriptine, which acts centrally to suppress hepatic glucose production and improve insulin resistance [130, 140]. The amylin analogue pramlintide is another centrally acting anti-diabetes drug that elicits a distinctly different set of effects via its receptor expressed by hindbrain neurons. These include reduced food intake and weight loss, decreased gastric emptying, and inhibition of glucagon secretion [130, 141]. While neither bromocriptine nor pramlintide is particularly effective or is in wide use, both offer proof-of-concept evidence that the brain can be targeted to treat diabetes in humans, although drugs that target both brain and periphery are currently far more efficacious.

Among these are synthetic GLP-1 receptor agonists, which are currently among the most potent anti-diabetes medications. Long-acting GLP-1 receptor agonists can be administered on a weekly basis and are especially effective in lowering HbA_{1c}; unlike insulin,

Table 10.2 Glucose-lowering agents and their site of action with specific reference to central effects.

Medication name	Site of action	Mechanism of action	References
Insulin	Muscle, adipose tissue, liver, brain	• Facilitates entry of free fatty acids and glucose into muscle and adipose tissue • Increases hepatic glycogen synthesis while inhibiting hepatic glucose output via both a direct action on hepatocytes and an indirect mechanism involving the brain	[130–132]
Metformin	Liver	• Lowers hepatic glucose production • Increases intestinal glucose utilization • Induces GDF-15, which acts in CNS	[133, 134]
Sulfonylureas	Pancreas	• Stimulates insulin secretion by closing K_{ATP} channels on islet β cells	[135]
GLP-1 receptor agonists	Pancreas, intestine, CNS action	• Stimulates insulin release from the pancreas • Neuronal actions cause inhibition of glucagon secretion as well as gastric emptying and food intake, causing weight loss • May increase melanocortin signalling by activating POMC neurons	[136, 137]
SGLT-2 inhibitors	Kidney	• Inhibits glucose reabsorption in renal tubules, thus promoting glycosuria	[138]
Thiazolidinediones	Adipose tissue	• Promotes insulin sensitivity as well as adipocyte differentiation and triglyceride storage by activating the nuclear receptor PPARγ • A glucose-lowering effect mediated via hypothalamic neurons has been reported	[139]
Bromocriptine	CNS	• Dopamine receptor agonist acts centrally to promote glucose lowering	[140]
Pramlintide	CNS	• Acts in the area postrema to decrease gastric emptying and inhibit glucagon secretion	[141]

CNS, central nervous system; GDF-15, growth and differentiation factor-15; GLP-1, glucagon-like peptide 1; POMC, proopiomelanocortin; SGLT, sodium-glucose co-transporter 2.

they do so without weight gain (and often induce weight loss) and with minimal risk of hypoglycaemia [130]. GLP-1 receptors on pancreatic β cells are a key target for these drugs, activation of which augments glucose-induced insulin secretion. In addition, these agents can impact brain function in multiple ways [136]. Activation of GLP-1 receptors on vagal afferent fibres supplying the gastrointestinal tract induces satiety while reducing gastric emptying, and activation of hindbrain GLP-1 receptors can amplify this effect, with the combination leading to significant weight loss. Some POMC neurons also express GLP-1 receptors and increase firing rate, leading to increased melanocortin signalling in response to GLP-1 stimulation [142]. Whether these or other CNS effects promote glucose lowering independently of effects on food intake and weight is presently unknown.

Recent progress in this area includes the development and clinical testing of unimolecular dual- and tri-agonist compounds that combine GLP-1 with glucagon and/or gastric inhibitory peptide (GIP) into a single, long-acting peptide suitable for systemic administration [143]. One of these compounds recently received licensing approval for type 2 diabetes treatment. The dual agonist tirzepatide exerts glucose-lowering and weight loss effects that are more potent than other non-surgical options. Like GLP-1 receptor agonists, these drugs mediate their beneficial effects via actions on both pancreatic β cells and the peripheral and central nervous system.

Another recent development relates to metformin, a first-line drug for type 2 diabetes, with anti-diabetes effects that appear to involve a subset of hindbrain neurons. This inference is based on evidence that metformin induces expression of growth and differentiation factor-15 (GDF-15, also known as MIC-1) [133], a potent endogenous inhibitor of feeding [144, 145] that can be secreted by several cell types and tissues, typically in response to cellular stress [146–148]. The central effects of GDF-15 are mediated via the binding to its receptor, GFRAL, expressed uniquely by neurons in the area postrema and nucleus of the solitary tract [149–152]. Although the metformin-induced increase of circulating GDF-15 levels is modest (and below that needed to cause pronounced anorexia), the finding that in mice metformin's anti-diabetes effect is abrogated by GFRAL deletion [133] implies a requirement for GDF-15 and its action in the brain. As more is learned about the brain's role in glucose homeostasis and diabetes pathogenesis, successful targeting of the brain to improve diabetes management seems likely.

Conclusion

Growing evidence points to a key role for the brain, working in cooperation with pancreatic islets and other peripheral tissues, in the maintenance of blood glucose homeostasis. The brain's contribution to this process likely hinges on its ability to accurately sense and respond to changes in the circulating glucose level, and although our understanding of how this occurs remains limited, dysfunction of this sensing process may contribute to the progressive rise of the BDL_G during the transition from obesity to type 2 diabetes. Since it is now clear from pre-clinical studies that diabetes remission is achievable via strategies targeting the brain, future research is needed to translate these findings to the clinic. Ongoing drug development efforts that target the brain have the potential not simply to lower blood glucose levels, but to normalize the BDL_G in individuals with type 2 diabetes.

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11 Control of Body Weight: How and Why Do We Gain Weight Easier Than We Lose It?

Janine Makaronidis[1,2,3] and Rachel L. Batterham[1,2,3]

[1] Centre for Obesity Research, Rayne Institute, Department of Medicine, University College London, London, UK
[2] University College London Hospital (UCLH) Bariatric Centre for Weight Management and Metabolic Surgery, London, UK
[3] National Institute of Health Research, UCLH Biomedical Research Centre, London, UK

Key points

- Obesity is a chronic, remitting and relapsing disease that can lead to multiple debilitating physical and psychological complications.
- The causes of obesity are complex and multifactorial, including a combination of genetic susceptibility, epigenetic influences, and environmental factors, which all contribute to a biology that favours weight gain.
- Weight loss through energy restriction is followed by powerful physiological adaptations, aiming to defend the higher weight, which drive weight regain.
- Several environmental and physiological factors promote weight gain. Environmental factors, such as food cues and easy access to energy-dense palatable foods, support food choices that are driven by cognitive, social, and emotional factors.
- Exposure to food cues can alter secretion profiles of appetite-regulating hormones and activity in reward areas of the brain, in a manner promoting increased energy intake in an environment of excess energy availability.

Obesity is a chronic multifactorial disease, defined as an excess of adipose tissue, which adversely affects health. The worldwide prevalence of obesity, defined by a body mass index (BMI) of ≥30 kg/m^2, has risen by almost 30% in the past 30 years, which equates to over 2 billion people currently living with obesity globally [1]. Obesity-associated comorbidities, including type 2 diabetes, cardiovascular, renal, and liver disease, and certain types of cancer, have a substantial negative impact on quality of life, but also lead to a significantly increased mortality [2]. Consequently, the life expectancy of a person living with severe obesity (BMI ≥40 kg/m^2) is reduced by up to 14 years [3].

Despite the growing disease burden associated with obesity and its complications, public health interventions to date have been largely ineffective at reducing the rapidly growing prevalence of obesity, which on a global level is continuing to rise exponentially [2]. Until recently, treatment strategies have almost exclusively focused on restricting energy intake and increasing physical activity. Although these strategies result in weight reductions in the short term, they are followed by very powerful biological compensatory mechanisms aiming to defend a higher body weight [4]. These physiological mechanisms act beyond voluntary food intake and drive the weight gain that commonly follows weight loss through dietary energy restriction. In order to deliver more effective treatments for people living with obesity, a fundamental understanding of the processes regulating body weight, the genetic variations underlying weight heritability and predisposition to weight gain, as well as the environmental, behavioural, and societal factors that have an impact on weight at a population levels are required. Furthermore, elimination of the stigma and the societal discrimination against people living with obesity is essential. In this chapter we review the physiological mechanisms regulating weight, as well as the multiple biological, genetic, and environmental factors that affect weight, in order to explain why gaining weight is much easier than losing it.

Body weight regulation

Energy homeostasis: control of appetite and body weight

Appetite and body weight are regulated through an incredibly complex network of interrelated mechanisms, through which signals concerning energy need and availability are collected from peripheral tissues and integrated in the central nervous system (CNS) [5]. The areas of the CNS responsible for body weight control respond to the inputs they receive from the periphery, which include numerous metabolically active neuropeptides influencing appetite and energy storage and expenditure, in order to ensure that available energy meets the body's metabolic requirements [6].

The gastrointestinal (GI) tract and adipose tissue are the body's largest endocrine organs and have a key role in responding to energy needs and availability to regulate body weight and energy balance. Gut-derived signals convey information about the composition and energy content of ingested food to the CNS, whereas adipose tissue conveys signals relating to longer-term energy availability [7]. These signals are conveyed to the hypothalamus, the main CNS centre integrating peripheral homeostatic signals of energy availability into

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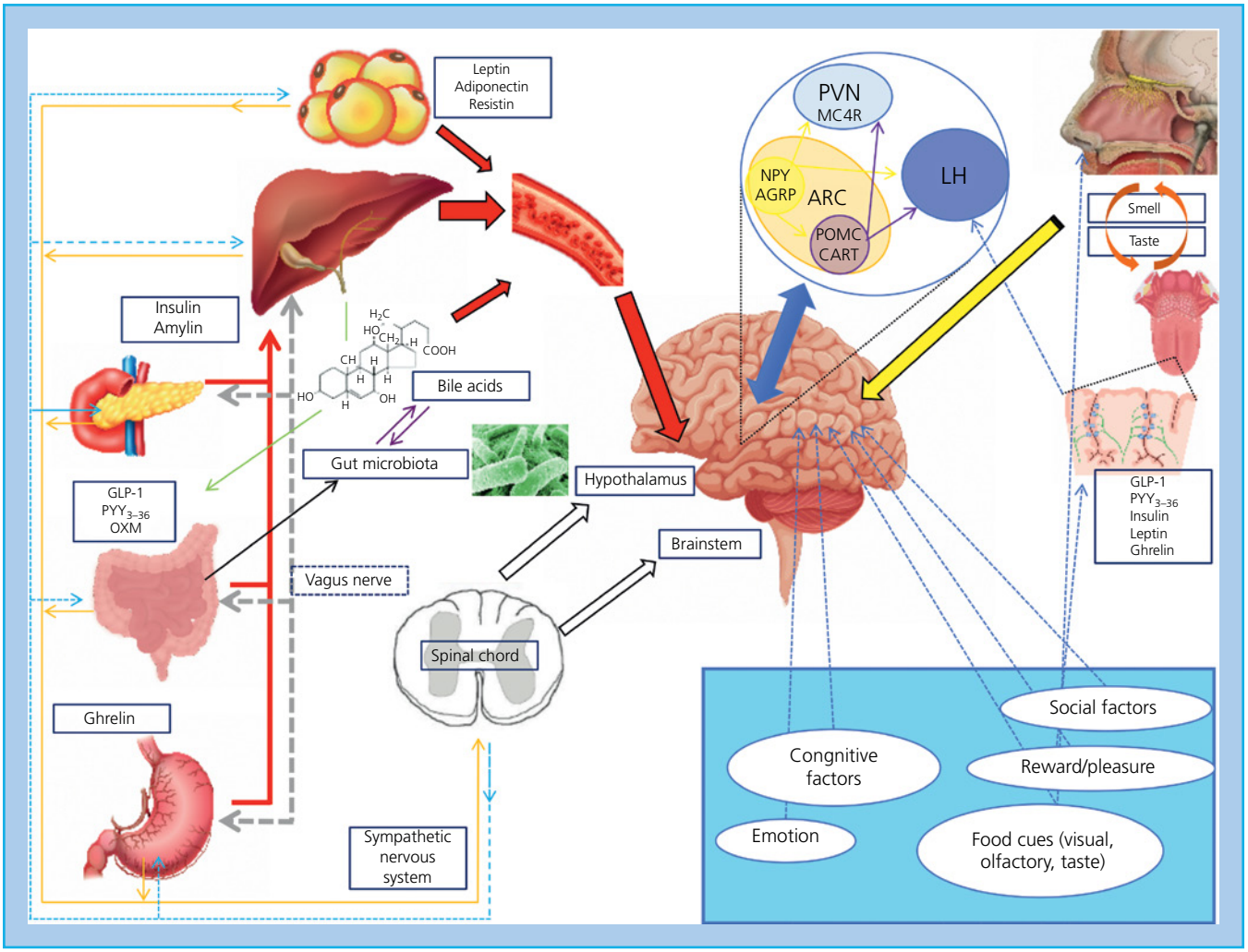

Figure 11.1 The regulation of eating behaviour. Schematic diagram illustrating the major processes involved in regulating eating behaviour. The brainstem and hypothalamus act as the first relay centres for neural and metabolic signals of nutrient availability. The hypothalamus then integrates peripheral signals of energy availability into the central nervous system [5]. In the arcuate nucleus (ARC) of the hypothalamus, neurons expressing neuropeptide Y (NPY) and agouti-related peptide (AgRP) drive orexigenic responses, whereas proopiomelanocortin (POMC) and cocaine- and amphetamine-related transcript (CART) neurons suppress appetite [8]. In the paraventricular nucleus of the hypothalamus (PVN), activation of the melanocortin-4 receptor (MC4R) promotes satiety. The lateral hypothalamus (LH) also receives inputs about the chemosensory properties of food. The appetitive network integrates information from food cues, such as sight, taste, and smell, reward-related information, and social and emotional factors with cognitive processes [5]. GLP-1, glucagon-like peptide-1; PYY, peptide YY3-36; OXM, oxyntomodulin. Source: Reproduced with permission from Pucci and Batterham 2019 [6].

central networks. This in turn generates feelings of either hunger or satiety, to drive a person's appetite and eating behaviour according to energy needs [5]. The processes involved in the control of eating behaviour are summarized in Figure 11.1.

Physiological regulators of body weight

Gut hormones

Gut hormones are metabolically active polypeptides, which are secreted by enteroendocrine cells along the entire length of the GI tract and have endocrine, autocrine, and paracrine functions [7]. Receptors for gut hormones are located on a multitude of organs and tissues, but most important for appetite regulation are those on the hypothalamus and other CNS regions involved in the control of eating [6]. In conditions of energy depletion, the hormone ghrelin is secreted from P/D1 cell populations predominantly in the gastric fundus [9]. Ghrelin is a growth hormone secretagogue and has potent orexigenic effects; when it binds to growth hormone secretagogue receptor type 1a (GHSR1a) in the hypothalamus, it increases appetite and promotes a desire and drive to eat [10]. A multitude of gut hormones are secreted in response to eating, which signal energy availability. Peptide YY 3-36 (PYY), glucagon-like peptide-1 (GLP-1), and oxyntomodulin are secreted from enteroendocrine L cells and have a key role in regulating energy and glucose homeostasis [7,11]. Within the hypothalamus, activation of their respective receptors suppresses appetite and generates a feeling of satiety, in an opposing manner to ghrelin [12].

Table 11.1 summarizes the role of the main hormones secreted along the GI tract in regulating appetite.

It is important to note that gut hormones act synergistically in the control of appetite and body weight. Administration of native peptide infusions of PYY, GLP-1, and oxyntomodulin (OXM) in human studies has shown that their effects on appetite suppression

Table 11.1 Gut hormones and their role in appetite regulation.

Hormone	Secretion from GI tract	Target	Effects on appetite
Ghrelin [9]	P/D1 cells in the gastric fundus, antrum, and duodenum in response to: Fasting Meal patterns Food cues	Following acylation, acyl-ghrelin binds to GHRS1a in the hypothalamus, VTA and other reward areas of the CNS, and the vagus nerve	Increased appetite Hunger Increased gastric emptying Increased reward value of food
PYY [12, 13]	Enteroendocrine L cells, following exposure to nutrients (protein and fatty acids)	Y2 receptors on the vagus nerve and throughout the CNS	Reduced appetite and energy intake Satiety Delayed gastric emptying
GLP-1 [14, 15]	Enteroendocrine L cells, following exposure to nutrients (glucose and fatty acids) and bile acids	GLP-1R are widely distributed on multiple organs and tissues including the hypothalamus, liver, skeletal and cardiac muscle, and vagus nerve	Reduced appetite and energy intake Satiety Delayed gastric emptying Insulin secretion
OXM [16]	Enteroendocrine L cells, co-secreted with GLP-1 following nutrient ingestion	GLP-1R and glucagon receptors OXM also directly acts on the hypothalamus (unknown receptor)	Reduced appetite and energy intake Satiety
CCK [17]	Enteroendocrine I and L cells in response to nutrient intake (lipids and protein)	CCK-1 receptors along the GI tract (stomach, pancreas, gallbladder) and CCK-2 receptors in the CNS	Reduced appetite and energy intake Satiety Delayed gastric emptying Insulin secretion
GIP [18]	Enteroendocrine K cells in response to glucose and lipid ingestion	GIP receptor on pancreatic islet cells, adipose tissue, and the hypothalamus	Reduced appetite and energy intake Insulin secretion
Neurotensin [19]	Enteroendocrine cells in response to nutrient ingestion, mainly lipids	NTR1, NTR2, NTR3 across the CNS, but particularly the hypothalamus and along the GI tract	Suppresses appetite Reduces GI motility Facilitates fat translocation
Uroguanylin [20, 21]	Intestinal epithelial cells in response to nutrient ingestion	GUCY2C receptor on intestinal epithelial cells and the hypothalamus	Suppresses appetite Satiety
Amylin [22]	Pancreatic β cells, co-secreted with insulin, in response to glucose and fatty acid ingestion	Amylin-specific calcitonin on the gastric fundus, throughout the CNS, and on bone	Suppresses appetite Promotes satiety Slows gastric emptying
Gastric leptin [23]	Gastric chief cells and endocrine P cells in response to energy intake, insulin, and CCK secretion	Leptin receptors on vagal afferents	Fasted state: increased appetite and energy intake Fed state: suppressed appetite

CCK, cholecystokinin; CNS, central nervous system; GHRS1a, growth hormone secretagogue receptor type 1a; GI, gastrointestinal; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; GLP-1R, glucagon-like peptide 1 receptor; GUY2C, guanylyl cyclase 2C; NTR, neurotensin receptor; OMX, oxyntomodulin; PYY, peptide YY 36; VTA, ventral tegmental area.

are additive, compared to each individual peptide in isolation [19, 24, 25]. In addition, cholecystokinin (CCK) and gastric inhibitory polypeptide (GIP) intensify the anorectic effects on GLP-1 [15, 17, 26].

Gut hormones further control appetite and eating behaviour via their effects on the vagus nerve. Receptors for gut hormones including PYY, GLP-1, CCK, and gastric leptin are located on vagal afferents [23, 27]. It is of note that expression of these receptors is subject to the vagus nerve's innate plasticity and is directly affected by nutritional state [28]. Vagal signals project to the nucleus tractus solitarius (NTS); from there they are conveyed to higher CNS centres.

Hypothalamus and neurotransmitters

The hypothalamus integrates peripheral signals of energy availability into the CNS. Afferent signals from the NTS project to the arcuate nucleus of the hypothalamus [29]. Distinct neuronal populations drive orexigenic and anorectic responses, respectively. Neurons expressing neuropeptide Y (NPY) and agouti-related peptide (AgRP) drive orexigenic responses, whereas proopiomelanocortin (POMC) neurons suppress appetite, in a mutually exclusive manner [30]. POMC neurones also coexpress cocaine- and amphetamine-related transcript (CART). The melanocortin melanocyte-stimulating hormone (α-MSH) activates the melanocortin-4 receptor (MC4R) in the paraventricular nucleus of the hypothalamus, promoting satiety, improving insulin sensitivity, and increasing energy expenditure [29]. Anorectic gut hormones including PYY, GLP-1, and OXM directly activate α-MSH neurons. In contrast, in conditions of energy deficiency, ghrelin stimulates NPY and AgRP secretion, which in turn inhibit MC4R, generating a feeling of hunger and a drive to eat [8]. Interestingly, MC4Rs have been located on enteroendocrine cells and may act as a further regulator of gut hormone secretion [31]. Furthermore, mutations causing loss of MC4R function result in hyperphagia, accelerated growth, and severe obesity from a young age [32]. Moreover, at the level of the hypothalamus, these signals of short-term energy availability are further integrated with signals of longer-term energy availability, originating from adipose tissue.

Adipose tissue

Adipose tissue is a metabolically active organ that secretes cytokines and adipokines that regulate energy homeostasis. Adipose tissue responds to changes in nutritional status and energy availability

and undergoes remodelling, a dynamic process affecting its metabolic functions. The adipokine leptin is secreted by adipocytes and acts as a signal of long-term energy stored in adipose tissue, and circulating leptin levels correlate with adipose tissue mass [33]. Leptin activates POMC neurons and simultaneously inhibits NPY/AgRP neurons [34]. Consequently, increases in adipose tissue mass will lead to higher circulating leptin levels, which in normal-weight rodents results in an increase in anorectic signals and a reduction in energy intake [35]. In people who are normal weight, increases in leptin following a positive energy balance result in appetite suppression, a reduction in energy intake, and an increase in energy expenditure [36,37]. In contrast, in conditions of energy deficiency, leptin levels reduce and adipose tissue releases energy for use by other tissues via lipolysis [35]. In addition to leptin's role as a long-term energy availability signal, adipocytes secrete leptin acutely in response to energy intake. Leptin also has a role in modulating reproductive function. Leptin regulates kisspeptin secretion, a neuropeptide that stimulates gonadotropin-releasing hormone–producing neurons, thereby effecting gonadotropin secretion [38]. Furthermore, the leptin receptor is expressed throughout the immune system and leptin acts as a mediator for both innate and adaptive immune responses, triggering secretion of pro-inflammatory immune cytokines [39].

In addition, the adipokines adiponectin and resistin also regulate body weight. Adiponectin has catabolic effects through stimulation of lipid oxidation, has anti-inflammatory effects, and improves insulin sensitivity, reducing body weight [40]. Resistin, in contrast, reduces insulin resistance and promotes weight gain [41]. The exact interaction of adipokines and cytokines secreted by adipose tissue, however, remains incompletely understood.

Furthermore, cytokines have attracted increasing interest in recent years with regard to their role in energy regulation. For instance, growth differentiation factor 15 (GDF15), an inflammation-induced cytokine encoded by the macrophage inhibitory cytokine 1 (*MIC-1*) gene, is expressed in almost all tissues, but high levels have been measured in human studies in the liver, pancreas, adipose tissue, and blood [42]. Interestingly, GDF15 has potent anorectic effects, mediated by downregulating NPY neurons in the hypothalamus and through direct action on the area postrema and the NTS, through pathways independent of MC4R function [43].

Intestinal microbiome

The intestinal microbiome comprises trillions of microbial populations. These microbial populations interact with human intestinal physiology and the host–microbiome interplay in the GI tract thereby has impacts on the physiology that regulates energy homeostasis [44]. Interactions between enteroendocrine cells and certain bacterial populations in the microbiome can directly affect gut hormone secretion, by influencing enteroendocrine cell secretion of PYY and GLP-1 in response to nutrient ingestion [45]. Microbiota also rely on ingested nutrients for their own metabolism and release short-chain fatty acids, a byproduct of microbial metabolism, which stimulates GLP-1 and PYY release [45]. The microbiome also responds to changes in weight, by altering both its composition and metabolic function. However, the degree to which changes in microbial populations *per se* can influence human body weight remains unknown. In summary, the mechanisms by which the microbiome affects human metabolism and weight control are complex and incompletely understood.

Beyond homeostasis: hedonic pathways

Eating constitutes a behaviour and, particularly in an environment where energy availability exceeds energy requirements, food-related decision making is influenced by factors beyond homeostasis and a person's net energy requirement. With the average individual being faced with over 200 food-related decisions per day, food choices are largely driven by cognition, food availability, palatability, and social and emotional factors [5]. The perceived reward of tasting or consuming a certain food can override the satiety signals generated from having met energy requirements. Reward-related responses can override homeostatic signals, leading to an energy intake beyond an individual's net energy requirements [46].

Interestingly, exposure to food cues, such as the sight or smell of food, can generate a metabolic response. Circulating gut hormone levels can directly influence the reward response to food and circulating ghrelin levels rise in anticipation of eating [46]. Neuroimaging studies using functional magnetic resonance imaging (fMRI) have provided insight into the relationship between gut hormone profiles, food cues, and their reward value [6]. Reward centres in the CNS are highly responsive to the effects of gut hormones and exposure to food cues can directly activate these centres in the absence of an energy need [47,48]. Viewing food images or smelling food can directly stimulate ghrelin secretion and ghrelin levels directly correlate with CNS reward centre activity in fMRI studies [47,49]. In contrast, PYY and GLP-1 inversely correlate with reward responses to food cues and secretion of these hormones attenuates reward responses [15]. Circulating PYY levels rise following a meal and switch the control of eating behaviour from homeostatic to reward-driven control [13].

Importantly, gut hormones and their cognate receptors are also present in saliva, taste-sensing cells, and the olfactory bulb and likely modulate perceptions of the taste and smell of food, both of which are highly dynamic processes [50,51]. Ghrelin, for instance, modulates olfactory sensitivity, with circulating levels correlating with CNS olfactory activity [52]. GLP-1, ghrelin, and CCK are all expressed on lingual taste bud cells, suggesting they have a role in modulating taste sensitivity [50,51]. However, fMRI studies using cognitive tasks also demonstrate that goal-focused behaviour or cognitive processes can reduce food-related reward responses [53,54].

Metabolic alterations with weight gain

Weight gain occurs when energy intake chronically exceeds energy requirements. Weight gain results in several adaptive changes, including gut hormone secretion profiles, adipocyte function, the intestinal microbiome, as well as gustatory and olfactory functions [55]. It is likely that these changes predispose a person to further weight gain.

Gut hormone secretion profiles are altered with weight gain. Attenuated meal-stimulated secretion of anorectic peptides including PYY and GLP-1 is seen in obesity [12]. Ghrelin secretion profiles also become dysregulated following weight gain. Pre-meal peaks in circulating ghrelin levels are lost in obesity, combined with a reduced suppression of ghrelin secretion following a meal [9,12]. The cause of the dysregulation of ghrelin secretion and the pathogenesis of obesity remain incompletely understood. An increased number of ghrelin-expressing cells was seen in mice who gained weight after being fed a high-fat diet, compared to normal-weight controls. The number of ghrelin-expressing cells was compared to

genetically obese *ob/ob* mice, who had a lower number of cells compared to both mice fed a high-fat diet and normal-weight mice, suggesting that chronic exposure to a high-fat diet can dysregulate ghrelin physiology [56]. Furthermore, a recent study on stomach samples from people with obesity undergoing sleeve gastrectomy examined ghrelin cells in people with obesity compared to control samples from individuals who are normal weight obtained during gastroscopy [57]. Although the number of gastric ghrelin cells did not differ between the two groups, expression of ghrelin and its activating enzyme ghrelin O-acyl transferase (GOAT) was significantly higher in the samples from people with obesity, suggesting that ghrelin-producing cells are hyperactive in people with obesity. In addition, ghrelin expression positively correlated with glycaemic indices, BMI, and GOAT levels. The literature on whether people with obesity have increased populations of ghrelin-producing cells is inconsistent, with some studies reporting increased numbers of ghrelin-producing cells and other showing no difference in cell density between people with obesity and those of normal weight [58–60]. Taken together, these findings suggest that there may be multiple pathophysiological processes underlying the dysregulated ghrelin physiology in obesity.

Leptin levels initially rise with weight gain, along with adiponectin levels. Following prolonged weight gain, however, leptin signalling becomes impaired, which in turn inhibits further rises in adiponectin [40]. Resistance to the systemic effects of leptin and insulin eventually develops [61]. The elevations in leptin levels that follow weight gain do not result in significant increases in satiety signals or reductions in energy intake, suggesting that in people with obesity, either leptin acts as a signal rather than a regulator of body weight, or its function is overridden [62, 63]. Therefore, treatment with leptin supplementation is ineffective at producing significant weight loss in people with obesity [64]. Weight gain leads to increasing oxidative stress within adipocytes, with increased secretion of pro-inflammatory cytokines including tumour necrosis factor (TNF)-α and interleukin-6 [65].

Changes to the intestinal microbiome are also seen following weight gain, with reduced diversity in populations of microbiota in obesity. Furthermore, dysbiotic bacterial populations linked to obesity can increase energy absorption from ingested food [66]. Unfavourable microbial populations contribute to weight gain through farnesoid X receptor (FXR) signalling. Dysregulated secretion of bile acids, which are also FXR ligands, is also seen following weight gain [44]. These changes in the microbiome are likely to have an impact on enteroendocrine cell function; however, it remains unknown whether changes in microbiota have a causative effect or are a mere consequence of weight gain.

Importantly, despite insulin and leptin resistance and the dysregulation in enteroendocrine cell function and gut hormone secretion, sensitivity to the effects of PYY, GLP-1, and OXM from exogenous administration is preserved, which highlights the therapeutic potential of these peptides as treatment modalities for people with obesity [12, 25].

Compensatory mechanisms in response to weight loss

Although energy restriction in the short term will result in reductions in body weight, weight loss triggers powerful physiological responses aimed at defending the original higher body weight, which result in weight regain in the longer term [4]. A landmark study by Sumithran et al. investigated the impact of a 10-week very low-calorie diet (VLCD) on gut hormone secretion profiles [67]. At the end of the 10-week diet, significant reductions in circulating PYY, CCK, insulin, leptin, and amylin levels were seen, combined with increased circulating levels of ghrelin and GIP, which persisted over a 52-week follow-up period. Increased circulating ghrelin levels, coupled with increased appetite levels persisting beyond the original weight loss period, have also been demonstrated in people with obesity who maintained weight loss [68]. Consequently, within the CNS, expression and activity of NPY/AgRP neurons increase, whereas POMC activity decreases, further increasing the motivation to eat [69]. fMRI studies illustrate increased reward responses to food cues following periods of diet-induced weight loss. Recent fMRI study findings also suggest reward region activation could be used to predict longer-term outcomes of weight loss interventions [70, 71].

Changes in energy expenditure are also among the compensatory mechanisms that follow weight loss from energy restriction. Energy expenditure decreases through reductions in resting metabolic rate and reductions in thyroid hormone availability and sympathetic tone, which result in an increased ability of peripheral tissues to take up energy, combined with a reduction in energy expenditure [72]. Weight loss also drives metabolic responses within adipocytes themselves. The decline in adipocyte size as a result of weight loss alters their metabolic and inflammatory characteristics, which consequentially favour storage of ingested energy [73]. When adipocytes shrink, the growing extracellular matrix (ECM) causes mechanical stress to build up between adipocytes and the surrounding ECM, triggering inflammation and oxidative stress. In energy-deficit conditions, available energy may not suffice for ECM remodelling around the smaller adipocyte size, inhibiting lipolysis and driving the cell to reaccumulate fat in order to return to its original size [74].

Studies linking metabolic profiles with patterns of weight regain illustrate the association between adaptations to weight loss, weight regain, and the individual variability that exists in the response to energy-deficit diets. Weight loss maintenance following a VLCD has been linked to higher post-prandial PYY and GLP-1 levels [75]. In contrast, weight regain following a total diet replacement diet was associated with lower baseline GLP-1 levels and further reductions in GLP-1 after weight loss [76]. To date, substantial methodological differences still hinder direct comparisons in the outcomes of these studies, but evidence is emerging on how different lifestyle interventions are affecting an individual's physiology. For instance, exercise regimens may counteract some of the ghrelin rises seen following energy restriction and also increase PYY secretion [77, 78]. Different approaches to dietary interventions may also have differential impacts on gut hormone profiles. Reductions in ghrelin have been seen with high-protein, low-carbohydrate diets and ketogenic diets, which can also suppress appetite [79, 80]. Taken together, these findings suggest that individualizing lifestyle intervention based on a person's gut hormone profile could improve outcomes and weight gain maintenance in the first steps of obesity treatment algorithms.

Weight loss maintenance insights from bariatric surgery

Bariatric surgery, to date, is the most effective treatment for people with severe obesity. The Roux-en-Y gastric bypass and sleeve gastrectomy are the most commonly performed procedures worldwide

and lead to marked and sustained weight loss in the long term, combined with improvement or remission of obesity-related comorbidities such as type 2 diabetes [81]. In contrast to lifestyle interventions, people following bariatric surgery experience a significant change in eating behaviour, characterized by a reduction in hunger, increased satiety, changes in food preference away from energy-dense food, and changes in their senses of smell and taste [82, 83]. These eating behaviour changes lead to a reduction in energy intake, which drives weight loss. In stark contrast to dietary energy restriction, bariatric surgery results in changes in systemic physiology that favour weight loss maintenance. Bariatric surgery therefore offers a unique research opportunity to further our understanding of the physiology of weight loss maintenance in order to develop new and effective management strategies for obesity. Figure 11.2 compares the metabolic effects of energy restriction to bariatric surgery.

Remarkably, bariatric surgery leads to reversal of several pathophysiological aspects of obesity: for instance, meal-stimulated gut hormone profiles change, there are improvements in inflammatory changes, as well as a more favourable intestinal microbial profile [84]. These changes are brought upon through the anatomical changes to the GI tract from the surgical procedure, hence physiological responses also differ between the two procedures. In Roux-en-Y gastric bypass, the stomach is bypassed through creating a small pouch, which is anastomosed with the mid-jejunum [85], allowing ingested nutrients to bypass the stomach, duodenum, and proximal jejunum. Sleeve gastrectomy involves removal of 80–90% of the stomach [86]. Roux-en-Y gastric bypass results in a marked rise in meal-stimulated circulating levels of PYY, GLP-1, and other anorectic peptides; these changes are also seen post-sleeve gastrectomy but to a lesser extent [87]. Sleeve gastrectomy, by means of removing most of the ghrelin-producing cell population, leads to a significant reduction in ghrelin levels. However, responses to bariatric surgery are highly variable and follow a broad normal distribution [88]. Individual variability has also been correlated to meal-stimulated gut hormone profiles, with poor responders having lower levels of meal-stimulated GLP-1 and PYY [88]. Understanding the causality of this variation will provide valuable insights into developing improved and individualized approaches in the treatment of obesity and type 2 diabetes.

Genetic factors

Evolutionary perspectives

Metabolic pathways that control body weight have evolved over thousands of years. Eating is critical to survival and therefore it is hardly surprising that it has evolved to be inherently rewarding [89]. Metabolic and reward-related processes at the level of CNS centres regulating behaviour, including eating behaviour, are subject to evolutionary changes over time. Orientation to locate food, the ability to consume large quantities of food when this was available, as well as the ability to store energy for this to be mobilized when food was unavailable were once critical for survival. Mutations to favour an increased ability to store energy are seen in multiple species. MC4R mutations linked to increasing appetite and resisting starvation have been identified in animals adapting to nutrient-poor environments [89]. The human race, as well as most species, for the majority of its history lived and evolved in conditions of scarce energy availability. Our environment has only changed to conditions of permanent and surplus energy availability over the past few decades, creating a significant gene–environment mismatch.

Excess adiposity in our current environment where food is permanently available in surplus has been termed 'a normal response to an abnormal environment' [90]. However, although susceptibility is largely determined by genetic factors, environmental, epigenetic, social, and cultural factors determine phenotypic expression [91]. The following sections of this chapter review the evidence on genetic predisposition and the multiple additional factors contributing to an individual's weight and obesity risk, which are summarized in Figure 11.3. Further information about the genetics of obesity is found in Chapter 13.

Monogenic obesity

Monogenic obesity accounts for approximately 7% of cases of severe early-onset obesity [92]. The impact of single-gene loss of function highlights the role of these respective genes and proteins in the regulation of body weight. Understanding the physiological consequences of loss of function has important implications for developing novel management strategies for obesity.

Leptin and leptin receptor mutations

Loss-of-function mutations of the leptin gene, resulting in congenital leptin deficiency, lead to severe obesity from a very young age [93]. Leptin deficiency can be successfully treated with recombinant human leptin, which reverses the associated metabolic abnormalities. Interestingly, a case report of a individual with leptin deficiency receiving supplementation highlights that treatment with leptin resulted in significant rises in meal-stimulated GLP-1, PYY, and insulin levels, as well as reductions in ghrelin levels [94]. This illustrates the regulatory effect of leptin on ghrelin secretion and the interplay between leptin, GLP-1, and PYY. Mutations in the leptin receptor gene account for up to 3% of cases of severe obesity [93].

MC4R melanocortin-signalling pathway mutations

A series of mutations disrupting melanocortin signalling have been identified in humans. MC4R mutations cause 5–6% of cases of early-onset severe obesity [32]. MC4R gene mutations of varying functional significance are present in approximately 1 in 1000 adults in the UK [95]. The degree of receptor dysfunction correlates with the clinical phenotype. Loss-of-function mutations cause early-onset obesity, accelerated growth, and hyperphagia.

POMC null mutations also cause early-onset obesity, hyperphagia, and adrenocorticotrophin (ACTH) deficiency. Heterozygous mutations resulting in loss of function in melanocortins, however, increase the risk of obesity, but do not invariably cause obesity clinically [32]. The prohormone convertase 1 (PCSK1) has a role in converting POMC to ACTH, which is then further converted to α-MSH. PCSK1 mutations lead to severe obesity, hypogonadotropic hypogonadism, post-prandial hyperglycaemia, and, in infants, small intestinal malabsorption, which highlights that melanocortin signalling has a role in enteroendocrine cell function [96, 97].

Other monogenic causes

Further, rarer monogenic causes of obesity involve genes encoding proteins downstream of MC4R, including brain-derived neurotrophic factor (BDNF) and single-minded 1 (SIM1), a transcription factor involved in the development of hypothalamic nuclei [93]. The autosomal recessive Bardet-Biedl syndrome is characterized by

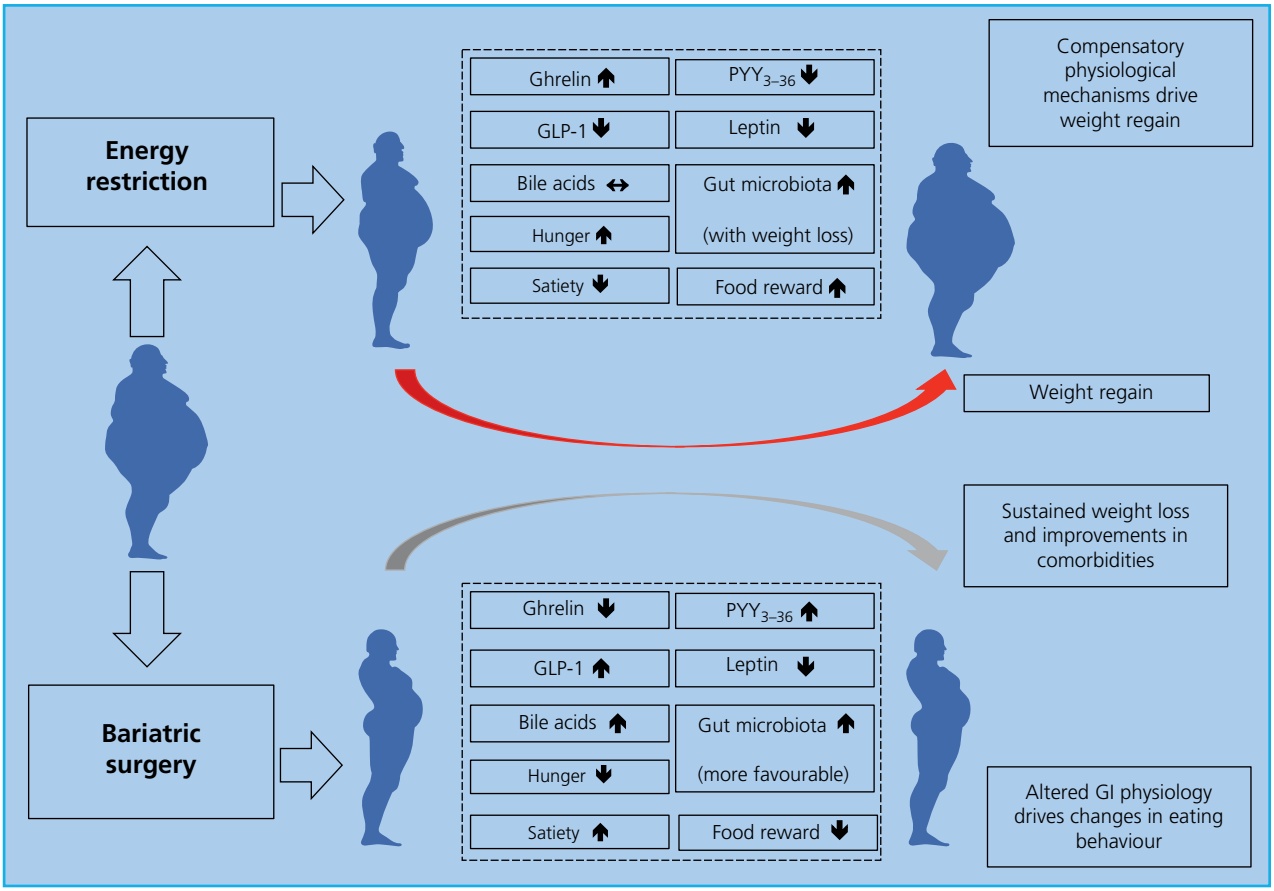

Figure 11.2 Physiological changes following energy-restriction diets compared to bariatric surgery. Weight loss caused by energy-deficit diets is followed by very powerful physiological adaptations that defend the original higher body weight and drive weight regain [4]. Circulating ghrelin levels rise and individuals report increased appetite. Circulating post-prandial levels of glucagon-like peptide-1 (GLP-1) and peptide YY3-36 (PYY) are reduced, leading to reduced perceived satiety. Brain response to food cues, assessed using functional imaging, increases in reward regions. These changes drive the weight regain that commonly follows weight loss through lifestyle interventions [4]. In contrast, bariatric surgery leads to a multitude of changes in gastrointestinal (GI) physiology, as a result of the altered GI anatomy and/or nutrient transit from the surgical procedures [82]. Post-prandial levels of GLP-1 and PYY are elevated and ghrelin levels are reduced. Favourable changes are seen in the microbiome. Individuals report reduced hunger, increased satiety, a shift in food preference away from energy-dense foods, and the brain's response to food cues is reduced. These changes lead to a change in eating behaviour and a reduced energy intake, which drive weight loss [4].

ciliary dysfunction causing obesity, learning difficulties, polydactyly, retinal dystrophy, hypogonadism, and renal disease [98].

Polygenic susceptibility to obesity

The heritability of weight has been well established, from studies on families, twins, and jointly or separately housed siblings, reporting heritability estimates of up to 70% [91]. Genome-wide association studies (GWAS) have identified over 97 BMI-associated genetic loci [99]. The strongest association between these single-nucleotide polymorphisms (SNP) and BMI comes from the obesity-risk variant of rs9939609 of the fat mass– and obesity-associated (*FTO*) gene. The high-risk AA variant is linked to increased appetite levels and preferences for energy-dense foods, and those with the AA variant are on average 3–4 kg heavier than those without the risk allele and have a 1.67-fold increased risk of obesity [100]. Adults of normal weight homozygous for the obesity-risk rs9939609 variant have higher post-prandial circulating ghrelin levels, increased hunger, and altered responses to food cues in CNS reward regions, compared to people with the low-risk variant [101]. While our understanding of these genetic variants remains limited, a recent meta-analysis concluded that GWAS-identified genetic variants only explain approximately 6% of population-wide variance in BMI [102]. A novel prediction tool for genetic susceptibility identified a 13 kg gradient in weight and a 25-fold gradient in risk of severe obesity across the polygenic score's deciles [103]. While the degree to which these polymorphisms explain the heritability of BMI remains incompletely understood, it is hypothesized that epigenetic factors may account for at least part of this gap in clarifying BMI heritability [104].

Epigenetic factors

Over recent decades, environment- and lifestyle-driven changes on a background of a strong genetic susceptibility have led to a rising prevalence of obesity [105]. Within population cohorts of people sharing the same environment only a subset develop obesity, and epigenetic studies have offered some insights into understanding weight gain through the interaction of genes and environment. Epigenetic studies have highlighted that, beyond an individual's genome, several factors influencing gene expression have an impact on weight and the risk of developing obesity [106]. The main

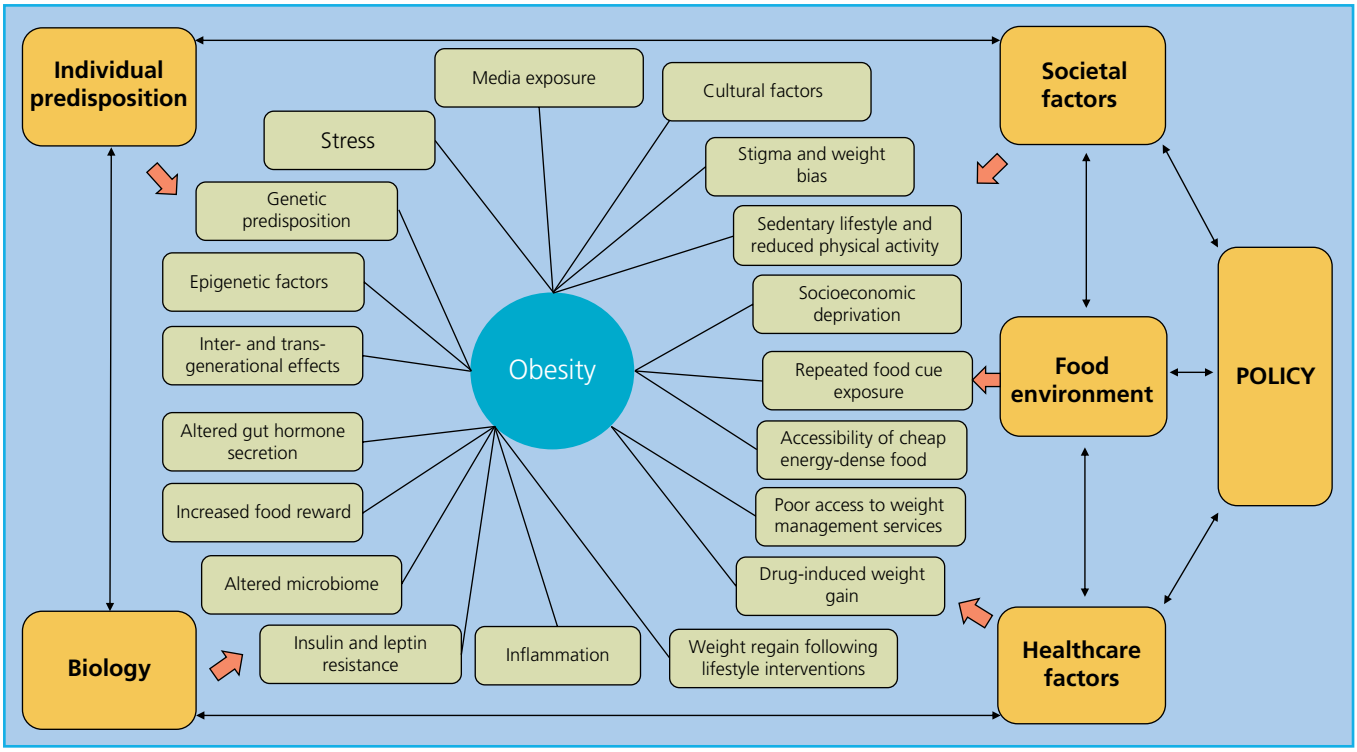

Figure 11.3 Factors contributing to the rising prevalence of obesity. The causes of obesity are numerous and multifactorial. The risk of obesity is an interplay between an individual's genetic predisposition, combined epigenetic factors, environmental exposures, their food environment, as well as social and cultural factors, which determine phenotypic expression [55].

epigenetic mechanisms involve DNA methylation, histone modification, and non-coding RNA, which can be passed on either through cell division (mitotically) or through transgenerational inheritance (meiotically) [107].

Environmental factors drive epigenetic changes in parental reproductive cells, in the intrauterine environment during fetal development, as well in as the perinatal period, which all play a key role in the development of physiological functions within every organ and tissue [107]. Gene expression may further be affected by environmental factors in childhood, up to and throughout adulthood. For instance, leptin gene methylation has been associated with maternal factors, such as maternal pre-conception weight, gestational weight gain, and gestational glycaemia and diabetes, which all contribute to offspring obesity risk [108, 109]. Similar changes in methylation, associated with obesity risk, have been described in the genes encoding adiponectin, POMC, and NPY [62, 110, 111]. Maternal factors during pre-conception and intrauterine development with potential implications for BMI have been associated with methylation changes in genes encoding insulin, immune cells, and growth factors [106]. A growing body of evidence now suggests that maternal nutritional status, stress, and exposure to smoking both in the peri-conception phase, during pregnancy, and during lactation significantly impact offspring obesity risk [112–114].

In addition to maternal factors, recent studies into epigenetic contributors to obesity have also highlighted paternal factors affecting intergenerational obesity risk in their offspring [115]. Increasing evidence suggests that paternal diet and obesity at the time of conception have impacts on the obesity risk of their children [112, 115]. Importantly, new evidence from animal models suggests that short-term changes in pre-conception paternal diet can alter offspring obesity risk [116].

Beyond the direct impact of maternal and paternal nutrition and health on the next generation, transgenerational epigenetic effects further influence obesity risk. An epidemiological study followed up two generations after exposure to intrauterine malnutrition during the Dutch famine of the Second World War. *In utero* famine exposure was associated with increased adiposity and adverse life outcome in the following generation [117]. Both maternal and paternal obesity have also been shown to have transgenerational effects in terms of increasing obesity risk in future generations; however, the link between paternal obesity and future generational obesity risk appears stronger compared to maternal obesity [118, 119].

Studies in weight-disconcordant monozygotic twins highlight the impact of environmental and epigenetic factors on weight and obesity risk [120]. Our epigenome is under constant interaction with the external environment and is continually influenced by environmental exposures. Dietary factors, exposure to toxins, exercise, and stress are among additional lifetime exposures with identified epigenetic consequences for weight and obesity in both childhood and adulthood [106].

Environmental and behavioural factors

Circadian rhythms, sleep patterns, and obesity

Human physiology changes throughout the day and all organs and metabolic processes are subject to diurnal variations and circadian rhythms. This also applies to several metabolic hormones that regulate glucose and energy homeostasis, including ghrelin, leptin, adiponectin, cortisol, and insulin [121–123]. Disruption in the circadian pattern of metabolic hormone secretion has been linked to obesity, and epidemiological data link sleep deprivation and

deranged sleep patterns with an increased risk of weight gain and obesity. Shift workers regularly working overnight, for instance, have an increased risk of developing obesity and night-time eating has been associated with food choices favouring energy-dense foods [10, 124]. Ghrelin secretion is higher in the biological evening compared to the morning, which in healthy adults correlates with hunger [121]. Disrupting this chronicity through a 12-hour behavioural cycle inversion led to higher post-prandial ghrelin levels, combined with increased cravings for energy-dense foods [121]. In a high-fat diet–induced obesity rat model, obesity was associated with altered diurnal rhythms in secretion profiles of GLP-1 and PYY, which occurred prior to loss of glycaemic regulation and persisted even when animals were eating the same amount of calories, suggesting that obesity *per se* can alter the chronobiology of gut hormone secretion profiles [125].

In addition to reversal of sleep patterns, sleep deprivation and fragmentation have both been associated with metabolic hormone dysregulation and weight gain [14]. GLP-1 levels reduce following sleep fragmentation, correlating with lower satiety levels [126]. Sleep deprivation is not only associated with a higher energy intake and reduced insulin sensitivity, but also with a reduction in the amount of weight lost during dietary interventions [127–129]. Sleep duration has been linked to higher weight loss and improved weight loss maintenance in people with obesity undergoing lifestyle interventions [130, 131]. The effect of sleep duration on weight is particularly evident in adolescents, where sleep duration has a strong negative association with BMI, independent of other obesity risk factors [132]. Taken together, these findings suggest that sleep has a role in the preservation of fat-free mass.

The timing of energy intake affects the metabolic control of energy homeostasis. Late eating has been linked to decreased energy expenditure, decreased carbohydrate utilization, and reduced insulin sensitivity [122]. In line with this finding, people who consume the majority of their daily energy intake early in the day have a lower risk of developing overweight or obesity [133]. Maintaining a regular meal pattern throughout the day with the majority of energy intake early in the day, combined with fasting periods overnight, leads to metabolic benefits, including reduced inflammation and a more favourable microbiome profile [134]. Furthermore, a recent systematic review and meta-analysis of intermittent fasting interventions in adults with overweight and obesity demonstrated that intermittent fasting, at least in the short term, had benefits in terms of body weight reductions [135].

The effect of dietary composition

It is without doubt that the increased food availability in the modern environment and the contact exposure to food cues, on the background of genetic predispositions, are major drivers for the increasing prevalence of overweight and obesity. However, in addition to a consistently high energy availability, the type and composition of food also affect weight and risk of developing overweight and obesity. The energy density of available food has been associated with developing overweight and obesity. In particular, consumption of energy-dense nutrient-poor foods in childhood is directly related to weight gain and adult obesity [136, 137]. Furthermore, energy-dense nutrient-poor foods, despite the higher calorie content per gram of food, have been associated with increased post-prandial appetite, food cravings, and lower satiety [138]. Socioeconomic factors are also directly related to energy-dense food consumption during childhood and the risk of obesity in adult life, in parallel with the low cost of energy-dense foods [136, 139].

The impact of food processing has recently been the focus of clinical studies. Hall et al. demonstrated that in healthy adults, a diet comprising ultra-processed food results in weight gain and excess energy intake during *ad libitum* food consumption compared to a diet consisting of unprocessed food [140]. Further findings in this study highlighted that ultra-processed food was consumed faster and that GLP-1 levels were reduced after a two-week period following the diet [140]. Ultra-processed foods commonly have a higher sugar content compared to the sweetness of the taste stimuli they elicit during eating. Integration of sweetness information from taste processing is a strong predictor of the reward value of food [141]. Therefore, one proposed mechanism suggests that in ultra-processed food, a mismatch between sweetness and nutrient contents may disrupt the signalling of its nutritional content from the gut to the CNS and thereby promote excess energy intake [142].

Gene–environment interaction studies have identified consumption of sugar-sweetened beverages and a high intake of fried foods and saturated fatty acids as risk factors for weight gain and obesity in people with an underlying genetic susceptibility [143]. Furthermore, advances in nutrigenetics are beginning to highlight individual genetic variants that may elicit more favourable metabolic responses to diets with different macronutrient compositions [144]. It is evident that there is no universally effective dietary intervention to elicit and maintain weight loss for people living with overweight and obesity. Individualizing interventions based on individual responses remains the most adequate approach for medical nutritional interventions for obesity, until advances in the understanding of gene–environment interactions with respect to nutritional interventions allow further personalization of care [145].

Medications and toxins

With improved treatments for multiple conditions in recent years, a higher percentage of the population now take medical treatments for chronic diseases. Drug-induced weight gain is a common side effect and a considerable contributor to the rising prevalence of obesity. In several areas of medical practice, a growing range of pharmacotherapy options allows the choice of alternatives with a more favourable side-effect profile. Importantly, novel agents with beneficial effects on weight and cardiovascular outcomes for the management of type 2 diabetes now permit a move away from agents causing weight gain in people with type 2 diabetes and overweight or obesity. However, within multiple other areas of clinical practice drug-induced obesity represents a growing challenge, particularly related to the use of antiretrovirals and antipsychotics. These changes in weight have adverse impacts on morbidity and mortality, quality of life, and medication taking. Therefore, understanding the physiological drivers and offering interventions to prevent and/or treat drug-induced weight gain will be crucial both in terms of reducing obesity-related complications but also for outcomes relating to the underlying condition.

Antipsychotics

Antipsychotic-induced weight gain is an important side effect of treatment with first- and second-generation antipsychotic drugs. Importantly, weight gain is common and occurs quickly following initiation of the drug. According to a meta-analysis, the risk of clinically significant weight gain across a range of antipsychotics was estimated at ≥7% compared to placebo [146]. Weight gain of variable degrees is associated with almost all antipsychotic agents. Of second-generation antipsychotics, clozapine and olanzapine

carry the highest risk of weight gain, followed by others including aripiprazole, quetiapine, and risperidone [147]. A large trial of antipsychotic drug use showed that 30% of participants taking olanzapine gained 7% or more of their original body weight over an 18-month period [148]. The extent of duration of weight gain also varies between drugs: for instance, weight gain with clozapine has been described to continue for up to 46 months before reaching a plateau.

With regard to understanding the underlying processes driving weight gain, most data stem from olanzapine, as this is one of the most commonly prescribed antipsychotics and causes significant weight gain. Olanzapine directly stimulates appetite and leads to increased energy intake and adiposity [149]. These effects are more pronounced in people with lower baseline BMI and younger age [146]. Both olanzapine's and clozapine's orexigenic effects, although incompletely understood, are thought to be at least partially caused by the drugs' action on hypothalamic appetite-regulating networks. Olanzapine directly stimulates hypothalamic orexigenic neurons, whereas clozapine inhibits CART-expressing anorectic circuits [150]. Both olanzapine and clozapine reduce resting metabolic rate [151, 152].

Antiretrovirals

The introduction of antiretroviral therapy has transformed human immunodeficiency virus (HIV) into a chronic disease over the past 30 years. People with HIV on adequate antiretroviral therapy now have a life expectancy comparable to that of the general population. However, antiretroviral therapy is complicated by multiple metabolic side effects, including hyperglycaemia and type 2 diabetes, hyperlipidaemia, weight gain, and obesity. Importantly, whereas weight gain following initiation of antiretroviral therapy in underweight individuals and those within the normal BMI range reduces mortality, overweight and obesity in people with HIV are associated with a greater risk of metabolic complications compared to people without HIV. Most older agents including nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) were not directly linked to weight gain. However, the combination with tenofovir alafenamide has been associated with significant increases in weight [153, 154]. Protease inhibitors (PIs) have also been associated with weight gain and increases in adiposity compared to NNRTIs [155]. The newer class of integrase strand transfer inhibitors (INSTIs) have become increasingly used in HIV treatment due to improve tolerability and their lack of susceptibility to HIV drug resistance. INSTIs are, however, associated with marked increases in weight from baseline and compared to other antiretrovirals [156]. A pooled analysis of antiretroviral trials with respect to weight gain identified low CD4 cell count, higher viral load, female sex, and black race as risk factors for higher weight gain [156]. The same analysis demonstrated average weight gain of >5% in 37% of trial participants and >10% in 17%.

Although the exact mechanisms through which antiretroviral therapy causes weight gain are unknown, novel research studies are illustrating several pathways, including interactions with adipose tissue, gut hormone secretion, and direct effects on the hypothalamic circuits controlling weight and eating behaviour. HIV itself, as well as antiretroviral therapy, induces direct inflammatory changes within adipose tissue. Viral proteins are commonly deposited within adipose tissue and antiretrovirals directly exert effects on adipose tissue biology, including increased inflammatory markers, lipolysis, and insulin resistance [157]. These processes also result in increased ectopic fat deposition in the liver and pericardium. A mechanistic study into the metabolic effects of antiretroviral therapies in people receiving combinations of NRTIs, NNRTIs, and PIs demonstrated significantly higher levels of ghrelin in people with hypertriglyceridaemia compared to those with normal triglycerides [158]. The higher weight gain associated with INSTIs is suggested to originate due to their direct effect on hypothalamic appetite-regulation circuits. One proposed mechanism is that INSTIs directly inhibit MC4R, thereby directly generating an orexigenic response, as dolutagrevir can inhibit α-MSH binding to MC4R [159]. Although these mechanisms are yet not fully elucidated, there is a growing population of people living with HIV and obesity who face a higher risk of metabolic morbidity and mortality.

Antidepressants

Depression is among the most common mental health conditions and often coexists in people living with obesity. Although there is an association between depression and weight gain, certain antidepressant drugs also directly cause weight gain. Mirtazapine, citalopram, fluoxetine, sertraline, and paroxetine are among commonly prescribed antidepressants that have been associated with weight gain [160]. In a 10-year follow-up study, the incidence of >5% weight gain associated with antidepressant use was 11.2 per 100 person-years [161].

Other drugs

Further drugs associated with weight gain include mood stabilizers and anti-epileptic agents such as lithium, valproic acid, gabapentin, and carbamazepine [162].

Weight stigma and adverse impact on biology

People living with obesity frequently experience stigma, weight bias, and discrimination. The impact of stigma and weight bias on people living with obesity themselves, the rising prevalence of obesity, and the efficacy of obesity management strategies have been poorly understood and underestimated. Examples of weight bias include the notions that obesity is a lifestyle choice and that people living with obesity lack self-discipline, and are lazy or unmotivated. Internalized weight bias is highly prevalent even among the general population [163]. Weight stigma and bias have been reported in a multitude of settings including education, healthcare, and employment [164]. Exposure to weight bias and stigma leads to increased energy intake, exercise avoidance, and weight gain [164–167].

Furthermore, weight bias internalization adversely affects both mental and physical health [168]. Physiological mechanisms such as increased stress levels are likely to be driving these adverse effects on health. Exposure to stigmatizing stimuli increases cortisol reactivity in lean and overweight women [169]. Weight stigma was associated with obesity, risk of type 2 diabetes, depression and anxiety, cortisol levels, oxidative stress, and inflammatory markers in recent a meta-analysis [170]. There is now accumulating evidence suggesting that stigma directly contributes to the rising prevalence of overweight and obesity. It is therefore critical, as part of responding to the growing obesity epidemic, to provide fair, effective care for people living with obesity to eliminate weight stigma. A new public narrative challenging existing preconceptions, which is based on scientific knowledge, is necessary [171]. Incorporating strategies to address healthcare-related weight stigma is also required in treatment algorithms and guidelines for healthcare professionals caring for people living with obesity [172].

Effects of societal factors and policy

Factors contributing to the growing prevalence of obesity arise from multiple societal sources. Evidence suggests that regional differences even within the same country can lead to local variations in obesity risk [173]. Suggested factors contributing to obesity risk in children and adolescents include paternal obesity, paternal smoking, low physical activity levels, and media exposure [173]. Moving from a neighbourhood with high levels of poverty to an area of lower poverty reduces the prevalence of severe obesity [174]. A longitudinal UK cohort study identified parental obesity, high television exposure, weight gain in the first year, and short sleep duration as risk factors for childhood obesity [175]. Furthermore, food and beverage marketing increases dietary intake of energy-dense foods and beverages in children [176]. Carriers of the high-risk allele of the *FTO* gene, in particular, are highly susceptible to the effects of food marketing, compared to carriers of the low-risk variant [177]. Further societal factors identified as increasing the risk of weight gain and obesity include the increase of desk- and computer-based work across most occupations, reductions in physical activity, and increased screen time in the entertainment industry [55].

In order to reverse the obesity epidemic, implementation of effective individualized treatment strategies is required for people living with obesity, combined with preventive measures to reduce the rising prevalence of the disease. To be effective, policy changes would require the participation of multiple sectors. The food environment in schools has been highlighted as a potential area for preventive policies to reduce obesity rates among school-aged children. To date, although studies are starting to demonstrate that regulating food standards can lead to significant reductions in energy intake during the school day, the longer-term impacts of such policies are not yet known [178]. Ensuring that the healthiest food choices for a given individual are also among the most accessible and affordable is among the World Health Organization's recommendations for obesity prevention [2]. Eradicating weight bias and improving knowledge of the science underlying weight gain and obesity among both the public and healthcare professionals are also critical [171]. Finally, available and accessible community and specialist-led obesity services, offering a range of services including nutritional and exercise therapies, psychological interventions, medical and surgical treatments, pre-conception advice and lifestyle modification, and antenatal care, as well as management of obesity-related complications using evidence-based and individualized approaches, will be necessary to improve obesity rates, care, and outcomes [55, 112].

Conclusion

The global prevalence of obesity has tripled since the 1970s and continues to rise exponentially. Obesity is a chronic, remitting and relapsing disease that can lead to multiple debilitating physical and psychological complications. Weight gain and obesity are undoubtedly highly complex and multifactorial. The reasons why we gain weight are multifaceted and involve a combination of genetic susceptibility, epigenetic influences, and environmental factors, which all contribute to a biology that favours weight gain. Due to the complex nature of obesity and the myriad factors affecting predisposition to weight gain and responses to weight loss interventions, individualizing treatment approaches will be essential. An increasing understanding of the complex interrelated mechanisms driving obesity is also necessary to offer effective treatments to people living with obesity, but also to implement successful preventive strategies.

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3 Pathogenesis of Diabetes

12 The Genetics of Diabetes

Rashmi B. Prasad[1,2]

[1] Lund University Diabetes Centre, Department of Clinical Sciences, Diabetes and Endocrinology, Lund University, Malmö, Sweden
[2] Institute for Molecular Medicine Finland (FIMM), Helsinki University, Helsinki, Finland

Key points

- Diabetes can be considered as a spectrum of disorders, with type 1 diabetes and type 2 diabetes as two ends of the spectrum and maturity-onset diabetes of the young (MODY), latent autoimmune diabetes in adults (LADA), and other types being the intermediates.
- Type 2 diabetes is a complex disease characterized by impaired insulin secretion, insulin resistance, or both and is caused by the intricate interplay between genetic, epigenetic, and environmental factors.
- Genetic architecture of a complex phenotype is defined by the number, frequencies, and effect sizes of causal alleles. Current understanding of the genetic architecture of type 2 diabetes points towards a combination of common single-nucleotide polymorphisms (SNPs), protective and rare variants, parent-of-origin effects, structural polymorphisms, and microRNAs, which can further be complicated by gene–gene and gene–environment interactions as well as epigenetics.
- The technical revolution in the field of genetics encompassing genome-wide association studies (GWAS) and next-generation sequencing has allowed identification of >1000 genetic variants in the risk for and protection of type 2 diabetes and many more with diabetes-related traits.
- Reported SNPs significantly associated with type 2 diabetes account for <20% of the heritability of type 2 diabetes. There may be several reasons for these shortcomings: too simple assumptions about the genetic architecture of the disease, ignoring additive and intrauterine effects, and restricting the analysis to only SNPs associated at 5×10^{-8}.
- The *CAPN10* gene on chromosome 10 encoding calpain 10 was the first type 2 diabetes susceptibility gene to be identified through linkage studies. The greatest success in linkage studies relates to the discovery of variants in *TCF7L2* as being associated with type 2 diabetes, but not the cause of linkage.
- The first candidate gene reproducibly associated with type 2 diabetes was *PPARG*, encoding the nuclear receptor PPAR-γ. The PPAR-γ receptor is a molecular target for thiazolidinediones, a class of insulin-sensitizing drugs used to treat type 2 diabetes, making it a compelling candidate gene.
- In 2007 several GWAS on type 2 diabetes were published. Uniquely, for the first time most of them reported associations to the same SNPs and genes: *TCF7L2*, *FTO*, *CDKAL1*, *HHEX*, *SLC30A8*, *IGF2BP2*, and *CDKN2A/2B*. These discoveries were therefore coined by *Science* as the Breakthrough of the Year 2007. Most of these variants have very modest risks. An exception comes from Greenland, where a common variant in the *TCFCB4* gene was strongly (odds ratio [OR] close to 10) associated with glucose tolerance as measured from an oral glucose tolerance test.
- The vast majority of type 2 diabetes–associated risk variants seem to influence β-cell function (e.g. *TCF7L2*, *CDKAL*, *SLC30A8*).
- While monogenic forms of diabetes (MODY) have been successfully ascribed to highly penetrant mutations in more than 10 genes, only a few rare variants have been associated with type 2 diabetes, among them rare variants in the *PAM* and *PDX1* genes.
- Also a few variants protecting from type 2 diabetes have been reported, including variants in the *SLC30A8* and *TCF2* genes. Mimicking how these variants protect from type 2 diabetes represents an ideal scenario for the development of new drugs.
- To describe the full genetic architecture of type 2 diabetes, a systems genetic approach will be needed combining GWAS, DNA methylation and histone modifications, and expression profiling including mRNA, proteins, and metabolites.

Increase in diabetes prevalence

Diabetes refers to a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both [1]. The chronic hyperglycaemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Diabetes is currently the fastest growing non-communicable disease. Worldwide prevalence figures estimate that there were 537 million people with diabetes in 2021, estimated to increase to 783 million in 2045 [2]. India and China have the highest reported prevalence rates of diabetes with 65 and 98 million in 2013, respectively, more than 90% of which is considered to be type 2 diabetes. In Europe, ~8% of the population is affected by diabetes, 90% of which is accounted for by type 2 diabetes, making type 2 diabetes the fastest-increasing disease in Europe and worldwide [3].

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The increasing prevalence of type 2 diabetes can largely be ascribed to the worldwide increase in obesity during the last 30 years; for instance, more than 60% of individuals older than 15 years in the UK and USA are overweight [4]. This has been attributed to a collision between genes and the environment. The social determinants of environmental factors tend to vary across populations and have changed rapidly over the last decades. A high energy–consuming lifestyle has been replaced by a Western sedentary one with little or no exercise and the consumption of an energy-dense diet. Meanwhile, genetic factors evolve at a slower rate across generations, and tend to favour the selection of *energy-saving thrifty genotypes*, which might have been beneficial for individuals living in times of unstable food supply by storing energy in times of surplus [5]. While this hypothesis provides an appealing explanation to the increase in obesity and type 2 diabetes, formal proof of it is still lacking.

Diabetes spectrum

Diabetes encompasses a range of heterogeneous metabolic disorders characterized by the inability of the body to assimilate glucose and maintain glucose homeostasis. Diabetes has been traditionally subdivided into type 2 diabetes and type 1 diabetes. However, this is an oversimplification of a rather complex situation. The concept of diabetes has grown over the past decades to the understanding that several different overlapping contributions from genetics and the environment can lead to manifestations of varying forms of disease. Contrary to being dichotomously distinct disorders, type 1 diabetes and type 2 diabetes can be considered rather as the two ends of a diabetes spectrum, with the intermediates comprising maturity-onset diabetes of the young (MODY), latent autoimmune diabetes in adults (LADA), and other subtypes.

Type 1 diabetes, also formerly known as juvenile diabetes or insulin-dependent diabetes, is a chronic condition that is due to autoimmune destruction of pancreatic β cells and is characterized by the (nearly) complete absence of insulin secretion and the presence of autoantibodies including glutamic acid decarboxylase (GAD) antibodies, leading to dependence on insulin injections. It is most often diagnosed in children, adolescents, or young adults under 35 years old. The incidence of type 1 diabetes varies based on geography, age, sex, and family history.

Latent Autoimmune Diabetes in Adults (LADA) is a common subgroup of diabetes accounting for ~7% of all individuals with diabetes in Europe. It is usually defined as GAD antibody–positive diabetes with onset after 35 years of age and no insulin requirement during the first six months after diagnosis [6–8]. LADA with high antibody titres is close to the type 1 diabetes part of the spectrum, whereas LADA with lower antibody titres is close to type 2 diabetes [9]. A family history of any form of diabetes is a strong risk factor for the development of LADA [10].

Maturity-onset diabetes of the young (MODY) refers to monogenic forms of diabetes with well-defined high-penetrance mutations in more than 10 different genes, and this number is still increasing (Chapter 20). The disease is characterized by autosomal dominant transmission of early-onset (<25 years) diabetes and varying degree of β-cell dysfunction [11]. It was long debated whether the MODY genes would harbour common, less-penetrant variants, increasing the risk of type 2 diabetes; now this seems to be the case for most of them, including *HNF1A*, *HNF4A*, *HNF1B*, *GCK*, and *PDX1* [12–14]. MODY shows extreme allelic heterogeneity, meaning that most MODY mutations are unique; to date, there are >200 mutations described in the *GCK* (MODY2) and *HNF1A* (MODY3) genes [15,16]. The appropriate diagnosis of MODY requires sequencing. With the advent of next-generation sequencing technologies, accurate MODY diagnoses are much more feasible today.

Maternally inherited diabetes and deafness (MIDD) is due to the A3242G mutation in mitochondrial DNA (mtDNA) [15,17]. As mtDNA is only transmitted from the mother, MIDD shows maternal transmission. In addition to hearing loss, many individuals also display neurological problems similar to individuals with the MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke), which is caused by the same mutation in mtDNA.

Neonatal diabetes is defined as diabetes with onset at birth or during the first six months of life and has both transient and permanent forms [15]. Mutations in several genes cause neonatal diabetes (e.g. *KCJN11*, *SUR1*, *GCK*, *INS*), and an appropriate genetic diagnosis is a prerequisite for optimal treatment. Individuals with mutations in the *KCJN11* gene do not only have severe diabetes but also developmental defects (DEND). These conditions are improved after switching from insulin treatment to treatment with large doses of sulfonylureas [18].

Diabetes can also develop secondary to pancreatic disease or other endocrine disorders and is referred to as *secondary diabetes*.

Type 2 diabetes is the most prevalent form, constituting 80–90% of all reported cases. It is the result of a complex interplay between genetic, epigenetic, and environmental factors. Type 2 diabetes develops when pancreatic β cells can no longer produce enough insulin to compensate for the insulin resistance, often imposed by increasing obesity. There is no formal definition of type 2 diabetes; individuals who do not fulfil criteria of type 1 diabetes, LADA, secondary diabetes, or monogenic forms of diabetes are considered to have type 2 diabetes. Type 2 diabetes is more often associated with increased age, wherein age of onset is usually over 35 years [19]. However, it is increasingly reported in adolescents in high-risk countries such as India and China [3]. The heritability of type 2 diabetes is discussed later.

All forms of diabetes represent a range of genetic aetiologies from the monogenic MODY variants to type 2 diabetes, which is a complex heterogeneous polygenic disease with a strong environmental component. The *ANDIS (All New Diabetics in Scania)* project in southern Sweden represents a new attempt to reclassify diabetes into subgroups based on genetic markers and biomarkers (Figure 12.1). A similar project has been initiated in Uppsala, Sweden, with the same goal (*ANDIU – All New Diabetics in Uppsala*).

Diabetes heterogeneity

Type 2 diabetes is diagnosed on the basis of one metabolite, glucose, and on the basis of exclusion criteria. If the individual does not have type 1 diabetes or monogenic diabetes, they are classified as having type 2 diabetes. However, this does not consider the underlying pathogenic causes or disease outcomes. Elevated glycaemia can be the consequence of multiple pathogenic processes occurring in myriad combinations, including rising insulin resistance and defective insulin secretion; consequently, type 2 diabetes is a heterogeneous disease [20]. Disease severity, progression, treatment strategies, and response can vary widely between individuals. The *palette model* of type 2 diabetes has been proposed, in which each person's individual risk for dysregulation in one or more component pathways

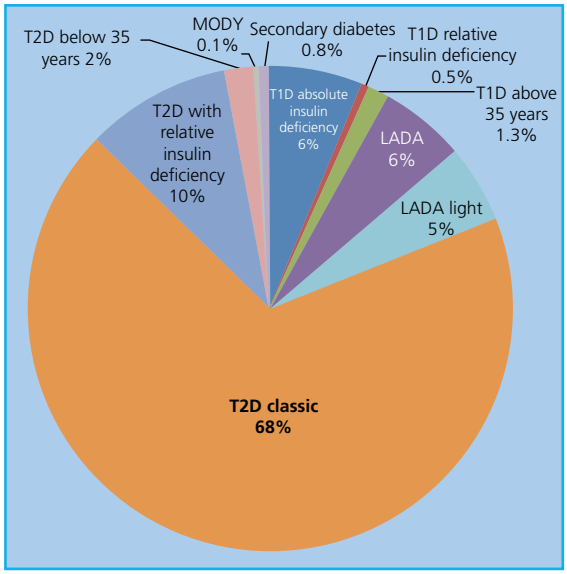

Figure 12.1 The spectrum of diabetes subgroups. The data are from the ANDIS project (All New Diabetics in Scania; http://andis.ludc.med.lu.se) in April 2012, which at that time included 5800 individuals with newly diagnosed diabetes aged 0–100 years. The criteria used for diagnosis are as follows: Type 1 diabetes (T1D): age at onset <35 years, C-peptide <0.2 nmol/l, and glutamic acid decarboxylase (GAD) antibodies >20; type 1 diabetes with relative insulin deficiency if C-peptide 0.2–0.6 nmol/l. Type 2 diabetes (T2D): age at onset >35 years, C-peptide >0.6 nmol/l, GAD antibodies <10; type 2 diabetes with relative insulin deficiency C-peptide 0.2–0.6 nmol/l. Latent autoimmune diabetes in adults (LADA): age at onset >35 years, GAD antibodies >20; LADA light if GAD antibodies 10–20. The data clearly illustrate the difficulty in classifying individuals with diabetes at diagnosis, with 19% unclassifiable. MODY, maturity-onset diabetes of the young.

can contribute to the overall development of type 2 diabetes [21]. Three primary approaches have emerged to address this heterogeneity. The first involves utilizing a set of clinical variables to divide individuals into subgroups based on manifestation of disease patterns. To this end, we performed data-driven machine learning on commonly measured clinical variables (age at diagnosis, sex, body mass index, glycated haemoglobin [HbA_{1c}], and homeostatic model 2 of assessment for insulin secretion [HOMA-B] and resistance [HOMA-IR]) in individuals with newly diagnosed diabetes. Five reproducible clusters were identified: severe autoimmune diabetes (SAID), which included both type 1 diabetes and LADA; severe insulin-deficient diabetes (SIDD); severe insulin-resistant diabetes (SIRD); mild obesity-related diabetes (MOD); and mild age-related diabetes (MARD). Each of these groups differed with respect to characteristics, risk of complications, and progression [22]. These subgroups were replicated in several populations [23,24] and are partially genetically different [25].

Given that phenotypes may vary across time and with different exposures, a second approach uses genetic information rather than phenotypes to subgroup individuals. This strategy minimizes the contribution of environmental factors and produces subgroups reflecting genetically driven pathways that predispose individuals differentially to type 2 diabetes–related metabolic disease outcomes [26]. A third approach combined both phenotype information including variables derived from oral glucose tolerance tests, magnetic resonance imaging (MRI)-measured body fat distribution, and liver fat content as well as genetic information, and identified six subtypes (implemented in individuals with prediabetes thus far) [27]. The subgrouping also opens up new avenues for research allowing better definitions of underlying pathogenic defects and refining of stratification. Moreover, more advanced methods using artificial intelligence and detailed phenotypes together with genetic information could allow for better subclassification and identification of individuals at high risk for the disease and development of complications [20,28,29]. Genetic studies into these subgroups would further help unravel their underlying pathophysiology.

Heritability of type 1 diabetes and type 2 diabetes

Heritability is a measure of the genetic influence on a particular trait. For type 1 diabetes, the risk in offspring of an affected mother is 2–4%, whereas the risk from an affected father is as high as 5–8% [30,31]. The sibling relative risk (RR) of type 1 diabetes is estimated at 15 [32–34]. Type 1 diabetes concordance in monozygotic twins is ~40%, but is dependent on age of diagnosis [35]. In twins with type 1 diabetes, the age at diagnosis was strongly correlated in identical pairs (RR = 0.94) compared to non-identical twins (RR = 0.59) [36]. Type 1 diabetes results from the interplay between genetic, epigenetic, and environmental factors. Genetic studies have reported >200 loci associated with type 1 diabetes, which explain ~80% of the heritability [19]. Environmental factors incorporate enterovirus infections, including viruses of the picorna family, as they are seen more often among individuals with newly diagnosed type 1 diabetes than in the general population, and they precede the appearance of autoantibodies, environmental pollutants, gut flora variations, and vitamin D exposure (Chapter 4) [37–39].

Type 2 diabetes clusters in families and the risk of developing type 2 diabetes depend on both genetic and environmental factors. Heritability parameters facilitate understanding of the genetic architecture of complex traits such as type 2 diabetes. However, heritability estimates have varied between 25% and 80% in different studies; the highest estimates are seen in those studies with the longest follow-up periods. The lifetime risk of developing type 2 diabetes is 40% for individuals who have one parent with type 2 diabetes and almost 70% if both parents are affected [40]. The concordance rate of type 2 diabetes in monozygotic twins is ~70%, while the concordance in dizygotic twins is only 20–30%. The proband-wise concordance rates (number of affected twins having a co-twin with diabetes) for monozygotic twins vary between 34% and 100% [41–44]. The relative risk for first-degree relatives – that is, the risk of developing type 2 diabetes if you have an affected parent or sibling compared to the general population – is ~3 and ~6 if both parents are affected [45]. However, these figures vary depending on the cohort and population studied.

The prevalence of type 2 diabetes varies widely among populations, from a few percent among White Europeans to as high as 50% among the Pima in Arizona [46]. While part of the observed ethnic variability could be attributed to environmental and cultural factors, some of the variation seems to depend on genetic differences.

Despite these reservations, there is no doubt the risk of type 2 diabetes is partly determined by genetic factors, many of which have already been identified, and while each identified variant explains only a very small proportion of the risk of type 2 diabetes in humans, overall they have contributed to our understanding of disease pathogenesis. One should also keep in mind that the variance explained by a risk allele in a population is not necessarily an indicator of its

importance in specific individuals, nor is it proportional to the affected pathway's importance or potential as a therapeutic target.

The more than 1000 SNPs identified explain less than 20% of the heritability of type 2 diabetes. There are many possible explanations for the missing heritability, including assumptions made about the genetic architecture of the disease and the definitions of heritability. The estimations of heritability explained assume that only additive effects determine disease risk and that the risk follows the liability threshold model; that is, that the genetic and environmental effects combine to form a normal distribution of liability and that disease arises in individuals surpassing a certain threshold in the distribution [47]. If these assumptions are not true, the estimate of heritability explained will not be correct.

Intrauterine effects can also affect heritability estimates because monozygotic twins are often monochorionic, which results in growth retardation compared to dizygotic twins, and low birth weight is associated with increased risk of type 2 diabetes later in life. Furthermore, there could be other explanations for the missing heritability problem. Heritability can only be estimated from the most recent generations for which information on affected status is available, whereas most of the variants studied thus far are ancestral variants hundreds of generations old. We do not know whether these ancestral variants (which have modest effects and have escaped purifying selection) can really explain the diabetes epidemic we see in the most recent generations or whether this can be ascribed to rare variants with stronger effects.

Moreover, heritability estimates are based on the *top* single-nucleotide polymorphisms (SNPs) from genome-wide association studies (GWAS); novel methods have been proposed that consider (i) a 0–1 scale as opposed to liability; (ii) ascertainment bias; and (iii) quality control of the GWAS SNPs. Estimating the proportion of variance explained by all SNPs in GWAS as opposed to only the most significantly associated SNPs could result in a more detailed estimate of heritability [48]. Applying an approach that considers all SNPs on the chip could in fact explain a much larger proportion of the *narrow-sense* heritability (>50%), supporting the existence of numerous yet unidentified loci with smaller effects [12, 49, 50].

Genetic architecture of type 1 diabetes and type 2 diabetes

The genetic architecture of a complex phenotype is defined by the number, frequencies, and effect sizes of causal alleles. Many hypotheses have been proposed to define the genetic architecture of type 2 diabetes: one hypothesis suggested that the unexplained heritability lies in a large number of common variants with low additive effects and that the disease represents the extremes of a normal distribution [51]. Another proposed that rare alleles might be responsible for effects observed with common variants (synthetic associations) and explain a majority of the heritability [52–54]. One argument against common and more so against rare variants is that they would have been removed from the population by natural selection [46]; however, this is not a valid argument for a disease like type 2 diabetes, where the penetrance of the genetic effect depends strongly on interactions with the environment, especially since this environment has changed in recent years and the genetic risk variants could have been neutral or even beneficial before the introduction of a Westernized lifestyle.

While extreme models are excluded by the present data based on epidemiological and linkage studies and GWAS, models wherein rare variants explain a little (<25%) or a lot (>80%) of heritability remain consistent [55]. Large next-generation sequencing studies in families will hopefully answer the questions about the role of rare variants in complex diseases. There is already substantial evidence for parent-of-origin effects on type 1 diabetes and type 2 diabetes risk, and studies are ongoing to explore this further. Structural polymorphisms and microRNAs add a further layer of complexity and have not yet been exhaustively studied.

The genetic architecture could also be influenced by gene–gene interactions (epistasis), where rare variants with high penetrance could act jointly with common alleles to increase the risk of disease. The extent of allelic heterogeneity seems to be less pronounced for the common forms of type 1 diabetes and type 2 diabetes than for monogenic forms like MODY. Moreover, there could be differences in the genetic predisposition to both type 1 diabetes and type 2 diabetes due to phenotypic heterogeneity within type 2 diabetes cases. For instance, in type 2 diabetes, lean people with type 2 diabetes are likely to carry a disproportionately high load of type 2 diabetes risk alleles [56].

Genetic loci for type 1 diabetes

GWAS have reported at least 257 variants mapping to 190 genes so far (Table 12.1). The main susceptibility genes currently accepted for type 1 diabetes are the human leucocyte antigen (HLA) class II alleles, and non-HLA loci including the insulin gene, *CTLA4*, *PTPN22*, interleukin 2 receptor a (IL2RA), and others [65]. Genes encoding HLA proteins are located within the major histocompatibility complex (MHC) on chromosome 6. The MHC is divided into class I, comprising HLA-A, -B, and -C; class II, comprising HLA-DR, -DQ, and -DP; and class III, comprising genes for complement components. HLA genes are highly polymorphic and variable between populations. Class II genes, especially DQ genes, are highly important for type 1 diabetes risk. Indeed, *HLA-DQB1* and *HLA-DRB1* on chromosome 6p21.3 account for ~50% of genetic susceptibility [66, 67].

A genetic risk score, which is a cumulative contribution of genetic factors to a particular trait in a specific individual, has been developed in type 1 diabetes comprising between 9 and 67 SNPs and has been a useful tool to discriminate between type 1 diabetes and type 2 diabetes or controls in Europeans. The first 9 SNPs that were used to create these genetic risk scores included SNPs tagging the high-risk HLA DR3-DQ2.5 (DR3)/DR4-DQ8 (DR4) alleles and the highly protective HLA DR15-DQ6.2 (DR15) allele. They had the highest effect size and contributed to a majority of the discriminatory power. These were also applicable to non-European populations, including India [68–70]. In addition, genetic risk scores were developed from loci showing specific associations with individuals with type 1 diabetes of African ancestry, which improved prediction of type 1 diabetes in this population [61].

Linkage studies for type 2 diabetes

The *CAPN10* gene on chromosome 10 encoding calpain 10, a cysteine protease with largely unknown functions in glucose metabolism, was the first type 2 diabetes susceptibility gene to be identified through linkage studies. Unfortunately, this locus has been difficult to replicate

Table 12.1 Type 1 diabetes susceptibility loci from genome-wide association studies [57–64].

No	beta	stdErr	chr	position	ref	alt	nearest_gene/locus	dbSNP	maf	Minor allele
1	0.7257	0.0152	6	31597875	A	G	PRRC2A	rs3130624	0.135	G
2	0.6274	0.0155	11	2184848	G	T	INS	rs3842727	0.3576	G
3	−0.6172	0.0129	1	114377568	A	G	RSBN1	rs2476601	0.0274	A
4	0.3647	0.0104	6	32682664	C	T	HLA-DQA2	rs9275601	0.4517	T
5	−0.2369	0.0086	12	111884608	T	C	ATXN2	rs3184504	0.1474	T
6	0.2255	0.0103	12	56445366	G	A	RPS26	rs10876866	0.2079	A
7	−0.4184	0.0173	10	6094697	C	T	IL2RA	rs61839660	0.0282	T
8	−0.1876	0.0086	2	204738919	G	A	CTLA4	rs3087243	0.369	A
9	1.8075	0.1169	6	31381610	C	T	MICA	rs566530443	0.0006	T
10	0.8488	0.0562	6	32623943	C	T	HLA-DQB1	rs554448117	0.0082	T
11	−0.1905	0.0094	16	11194771	C	T	CLEC16A	rs12927355	0.2716	T
12	0.7106	0.0502	6	32544901	T	C	HLA-DRB1	rs557673768	0.0014	C
13	1.4916	0.1056	6	33592294	G	C	ITPR3	rs74770208	0.0008	C
14	0.8981	0.0676	6	27863085	A	C	HIST1H2BO	rs114046480	0.0024	C
15	0.6709	0.0514	6	32500749	A	T	HLA-DRB5	rs529082000	0.0012	T
16	−0.2037	0.0129	18	12777325	T	C	PTPN2	rs7237497	0.1723	T
17	0.9061	0.0696	6	27604908	G	A	ZNF184	rs534914924	0.0022	A
18	0.6518	0.0501	6	32471012	G	A	HLA-DRB5	rs111637026	0.0146	A
19	−1.1275	0.0882	6	32434133	G	A	HLA-DRA	rs147168394	0.0044	A
20	0.6314	0.0496	1	114355237	G	A	RSBN1	rs55811970	0.0032	A
21	1.0269	0.0836	6	32557621	T	G	HLA-DRB1	rs201175797	0.0551	G
22	0.235	0.0182	6	33864137	G	C	MLN	rs6903171	0.1665	C
23	0.6612	0.0547	6	32535454	C	T	HLA-DRB1	rs555911977	0.0058	T
24	−1.5796	0.1311	6	30797717	C	T	DDR1	rs150558211	0.002	T
25	−0.1672	0.0114	10	90051317	A	G	RNLS	rs60888743	0.2837	G
26	1.5471	0.1303	6	32713511	C	CAGA	HLA-DQA2	rs113435733	0.0403	AGA
27	0.1867	0.0131	6	91005743	G	T	BACH2	rs6908626	0.0619	T
28	−1.8875	0.1621	6	32414007	T	G	HLA-DRA	rs182547608	0.0036	G
29	0.5433	0.0468	6	28338984	TTTTC	T	ZSCAN31	rs562339385	0.0032	–
30	0.7892	0.0692	6	32524259	A	G	HLA-DRB5	rs557987688	0.022	G
31	0.1568	0.0108	6	30932682	T	C	MUC21	rs2532924	0.4565	T
32	0.1352	0.0087	21	43836186	G	A	UBASH3A	rs11203203	0.1979	A
33	0.9839	0.0882	6	31571570	T	C	NCR3	rs115755747	0.0016	C
34	0.4972	0.0446	6	28602072	AC	A	SCAND3	rs147412566	0.0036	–
35	0.2226	0.0144	16	75252327	G	A	CTRB1	rs8056814	0.1809	A
36	0.132	0.0087	2	163110536	A	G	FAP	rs2111485	0.3393	G
37	1.3604	0.1275	6	29992561	T	C	ZNRD1	rs142808675	0.0008	C
38	−0.2173	0.017	15	79237293	C	T	CTSH	rs2289702	0.0769	T
39	−1.2227	0.1171	6	32716057	A	T	HLA-DQA2	rs140932748	0.0034	T
40	2.1216	0.2035	6	33415330	CTGGGGAAGGGGCACTGCTGTCCTGAT	C	ZBTB9	rs564240907	0.0012	–
41	0.5823	0.0564	6	32525686	C	T	HLA-DRB5	rs79071881	0.0453	T
42	0.1246	0.009	6	126674354	A	G	CENPW	rs2045258	0.4469	A
43	1.9175	0.1863	6	32472900	C	A	HLA-DRB5	rs560791209	0.0252	A

(*continued*)

Table 12.1 (*Continued*)

No	beta	stdErr	chr	position	ref	alt	nearest_gene/locus	dbSNP	maf	Minor allele
44	0.5998	0.0587	1	114154300	T	C	PHTF1	rs115985944	0.0032	C
45	0.1263	0.0088	22	30573552	T	C	LIF	rs1548389	0.2784	C
46	−0.6397	0.0631	11	2203649	G	A	TH	rs79889619	0.006	A
47	−0.3252	0.0225	19	10427721	T	A	FDX1L	rs74956615	0.014	A
48	−1.185	0.1174	6	31767898	G	A	VARS	rs184229371	0.0012	A
49	0.1168	0.0086	19	49206172	C	T	FUT2	rs516246	0.3207	T
50	0.6459	0.0651	6	32461525	A	G	HLA-DRB5	rs566515392	0.0014	G
51	−0.1219	0.0089	14	101306447	T	C	AL117190.2	rs56994090	0.3692	C
52	−0.1186	0.0088	9	4283137	G	T	GLIS3	rs1574285	0.4898	G
53	1.0205	0.1034	6	32523372	A	G	HLA-DRB5	rs557315642	0.0238	G
54	−0.128	0.0111	19	10462513	C	T	TYK2	rs11085725	0.2861	T
55	−0.1127	0.0088	16	28499291	A	G	CLN3	rs34835	0.3081	G
56	0.5065	0.0552	6	25711311	A	G	HIST1H2AA	rs113343204	0.0052	G
57	1.3728	0.1505	6	32554079	T	C	HLA-DRB1	rs545366210	0.0282	C
58	−0.1544	0.0122	1	206943968	C	A	IL10	rs3024493	0.0815	A
59	−0.1171	0.0107	4	123243594	A	ATC	KIAA1109	rs77516441	0.3922	–
60	0.1543	0.0121	12	112090022	C	A	BRAP	rs10744774	0.0871	C
61	−0.1045	0.011	16	20343091	T	C	GP2	rs4238595	0.1478	T
62	−0.1068	0.0087	18	67539392	T	C	CD226	rs1865761	0.4117	C
63	−0.1415	0.0117	19	47208481	T	C	PRKD2	rs425105	0.1426	C
64	0.9075	0.1022	6	32610888	C	A	HLA-DQA1	rs191251309	0.001	A
65	1.4048	0.1599	6	31031095	C	A	C6orf15	rs143610376	0.003	A
66	0.4436	0.0506	6	32524342	C	T	HLA-DRB5	rs561695641	0.0032	T
67	−0.1284	0.012	7	26905731	A	T	SKAP2	rs12540388	0.1314	T
68	−0.5023	0.0578	2	163124637	T	C	FAP	rs35667974	0.0024	C
69	0.1085	0.0091	20	1616206	A	G	SIRPB1	rs6043409	0.2029	A
70	−1.2666	0.1464	6	32349141	T	C	C6orf10	rs148551663	0.0026	C
71	2.9296	0.3409	6	32459111	A	G	HLA-DRB5	rs190437864	0.0116	G
72	0.8186	0.0959	6	32486903	T	G	HLA-DRB5	rs111233437	0.0539	G
73	1.4833	0.1758	6	31715815	A	G	MSH5	rs181227517	0.0004	G
74	1.1022	0.1311	9	135936325	C	T	CEL	rs541856133	0.0006	T
75	−1.1869	0.1416	6	32584902	G	C	HLA-DQA1	rs545211019	0.0026	C
76	−0.7999	0.0967	6	28259434	A	C	PGBD1	rs148484870	0.001	C
77	0.9823	0.1188	6	33281719	A	C	TAPBP	rs555991553	0.0294	C
78	1.1649	0.141	6	32714091	A	G	HLA-DQA2	rs149033708	0.0198	G
79	0.5775	0.0702	1	113860785	T	C	MAGI3	rs181871363	0.0026	C
80	0.7786	0.0952	6	32486366	C	T	HLA-DRB5			
81	−0.9059	0.1117	6	32041621	G	A	TNXB	rs6910390	0.0054	A
82	0.9938	0.1227	6	32458424	A	G	HLA-DRB5	rs555415494	0.0669	G
83	−1.1479	0.1419	6	30477991	A	C	HLA-E	rs28780109	0.001	C
84	0.1034	0.0109	14	69270891	A	G	ZFP36L1	rs1836984	0.2879	A
85	−0.1219	0.0128	4	166574267	A	G	TLL1	rs2611215	0.1817	A
86	−0.1026	0.0128	17	38073843	G	C	GSDMB	rs201413617	0.2728	C
87	0.0949	0.0088	22	37581677	C	T	C1QTNF6	rs229528	0.4615	T
88	2.5103	0.3164	6	32490351	G	T	HLA-DRB5	rs189165836	0.0168	T
89	0.5368	0.0677	6	32629199	T	C	HLA-DQB1	rs9273651	0.1178	C

90	−0.1042	0.0093	14	98488804	T	C	C14orf64	rs1456989	0.4966	C
91	0.6281	0.0802	1	113960679	G	C	MAGI3	rs72687922	0.0008	C
92	0.152	0.0141	11	2178995	C	T	INS	rs3842767	0.0325	T
93	0.1001	0.0105	4	26088128	G	A	RBPJ	rs16878091	0.1875	A
94	−0.112	0.0146	7	117086613	C	T	ASZ1	rs7795896	0.1941	C
95	1.0192	0.1334	6	32876806	A	C	HLA-DMB	rs183715617	0.0024	C
96	1.6406	0.2162	6	32433293	C	A	HLA-DRA	rs569394416	0.0012	A
97	−1.728	0.2278	6	29633183	A	AT	MOG	rs575293005	0.0006	T
98	−0.6529	0.0861	6	28843770	C	T	TRIM27	rs188021459	0.0016	T
99	0.0895	0.0097	11	128604232	G	T	FLI1	rs605093	0.3904	T
100	0.0939	0.0088	12	9910164	G	A	CD69	rs4763879	0.3129	A
101	−0.101	0.011	13	100079833	T	C	TM9SF2	rs9517712	0.2895	T
102	−0.3742	0.0501	11	2117063	T	C	IGF2	rs117996750	0.0066	C
103	0.4403	0.0589	6	33406405	C	T	SYNGAP1	rs45473295	0.0026	T
104	−0.1296	0.0136	10	6203983	C	T	PFKFB3	rs35420438	0.0771	T
105	−1.0726	0.1445	6	32339605	A	G	C6orf10	rs146129371	0.0014	G
106	0.107	0.0118	1	200798900	G	C	CAMSAP2	rs6690988	0.4189	C
107	2.6605	0.3609	6	32612877	C	T	HLA-DQA1	rs535836924	0.0006	T
108	0.7823	0.1065	6	33964794	G	T	GRM4	rs116071571	0.0048	T
109	0.4733	0.065	6	31293562	A	T	HLA-B	rs191989932	0.0026	T
110	0.0835	0.0098	10	33426147	T	C	NRP1	rs722988	0.4495	T
111	0.0819	0.0096	6	411064	A	G	IRF4	rs872071	0.3113	G
112	−0.1055	0.0106	17	44081064	A	G	STH	rs8070723	0.119	G
113	0.0957	0.0115	1	64109264	T	C	PGM1	rs2269240	0.2256	C
114	−0.0958	0.0126	12	9123932	T	C	KLRG1	rs7301381	0.3774	C
115	−0.461	0.0664	6	28075871	C	T	ZSCAN16	rs73396594	0.0587	T
116	0.4368	0.062	6	25404843	G	A	LRRC16A	rs112081434	0.0018	A
117	0.6553	0.0932	6	27220842	T	C	PRSS16	rs543638761	0.0006	C
118	0.2427	0.0343	7	51015193	T	C	GRB10	rs7780389	0.0493	T
119	0.6139	0.0878	6	30763526	C	T	IER3	rs187270848	0.001	T
120	−0.1116	0.0133	2	191953864	G	A	STAT4	rs6434435	0.1701	A
121	1.0574	0.1524	9	135997180	C	A	RALGDS	rs574287260	0.0004	A
122	2.0274	0.2931	6	32219430	G	T	NOTCH4	rs533733455	0.0032	T
123	2.0365	0.296	6	32486544	C	A	HLA-DRB5	rs565574629	0.0118	A
124	0.8942	0.1301	6	32134056	G	A	EGFL8	rs148091796	0.0012	A
125	−0.0837	0.0099	2	60608759	T	C	BCL11A	rs2540917	0.1665	C
126	0.6338	0.0934	6	29569407	C	T	OR2H2	rs140555963	0.0012	T
127	0.0846	0.009	6	159470242	G	T	TAGAP	rs212408	0.2929	G
128	−0.0926	0.0097	7	50477144	G	A	FIGNL1	rs10230978	0.2133	A
129	−0.2821	0.0422	10	72378489	C	G	PRF1	rs78325861	0.013	G
130	−182.86	27.364	8	47150073	C	T	SPIDR	rs139628162	0.0012	T
131	0.4251	0.064	6	29710026	G	A	HLA-F	rs147991173	0.001	A
132	−0.0855	0.0132	11	64107735	G	A	CCDC88B	rs663743	0.1983	A
133	−0.6521	0.0984	6	28731154	C	T	TRIM27	rs148907641	0.0024	T
134	0.0841	0.0106	10	6474353	A	T	DKFZP667F0711	rs617627	0.3582	T
135	−0.0857	0.0124	17	46029089	C	T	PRR15L	rs11651753	0.384	T
136	−0.331	0.0503	6	27600285	G	A	ZNF184	rs74759001	0.0074	A

(*continued*)

Table 12.1 (*Continued*)

No	beta	stdErr	chr	position	ref	alt	nearest_gene/locus	dbSNP	maf	Minor allele
137	−0.0825	0.009	2	100764087	T	G	AFF3	rs13415583	0.4113	G
138	0.093	0.0103	1	192537686	C	T	RGS1	rs1323295	0.229	C
139	−0.5907	0.0899	6	29225243	CT	C	OR14J1	rs201891037	0.003	–
140	−0.0823	0.0089	5	40521705	G	T	PTGER4	rs1876142	0.476	T
141	−0.0912	0.0132	8	120082941	A	C	COLEC10	rs13259300	0.3718	A
142	0.0797	0.0107	14	68753593	C	T	RAD51B	rs911263	0.4	C
143	1.9275	0.2962	6	27618463	A	G	HIST1H2BL	rs533910202	0.0004	G
144	−0.08	0.009	6	138003605	T	C	TNFAIP3	rs12665429	0.2929	C
145	1.1009	0.17	6	30773291	T	C	IER3	rs138484422	0.002	C
146	−0.0778	0.0087	5	35895725	A	T	IL7R	rs2303137	0.4978	T
147	0.1156	0.0127	1	120437884	A	G	ADAM30	rs2641348	0.1959	G
148	−0.1265	0.0162	1	198610536	A	G	PTPRC	rs75567729	0.0619	G
149	0.7392	0.1146	6	29042479	C	G	OR2B3	rs142977526	0.001	G
150	−0.6638	0.103	11	2086061	T	C	IGF2	rs188866230	0.002	C
151	1.1841	0.184	6	31556992	G	C	LST1	rs191504226	0.0016	C
152	−0.9103	0.1421	11	2204202	C	T	TH	rs144185922	0.002	T
153	−0.7821	0.1221	6	32554034	T	G	HLA-DRB1	rs536735233	0.0529	G
154	−0.0782	0.009	4	38604470	G	A	KLF3	rs337637	0.2626	A
155	−0.1011	0.0135	17	7633692	C	T	DNAH2	rs16956936	0.0751	T
156	−0.2647	0.0418	6	31648131	G	C	LY6G5C	rs535776589	0.3099	C
157	0.668	0.1058	6	29603538	A	G	GABBR1	rs180729352	0.0016	G
158	0.0896	0.0136	12	56395420	T	A	SUOX	rs773126	0.2374	A
159	1.263	0.2023	9	136079037	C	T	OBP2B	rs557297569	0.0004	T
160	0.5717	0.0917	6	32551289	G	T	HLA-DRB1	rs41284712	0.0304	T
161	1.6546	0.2657	6	32494958	C	T	HLA-DRB5	rs145153097	0.01	T
162	0.1034	0.0135	13	42902553	G	C	AKAP11	rs111368621	0.0911	C
163	1.5665	0.2534	6	33697559	C	T	IP6K3	rs563103984	0.0004	T
164	−0.0903	0.0135	10	8108382	C	T	GATA3	rs537544	0.3331	C
165	1.2394	0.201	6	31102304	G	A	PSORS1C1	rs182349224	0.0024	C
166	0.7409	0.1204	6	32841282	A	G	PSMB9	rs571941006	0.0014	G
167	−0.0776	0.0089	10	5926216	G	A	FBXO18	rs7919913	0.2432	A
168	0.0894	0.0108	10	6390450	G	A	DKFZP667F0711	rs947474	0.1861	G
169	−0.513	0.0835	11	2157279	G	A	IGF2	rs140848750	0.0038	A
170	0.2223	0.0362	6	28056250	G	T	ZNF165	rs17710827	0.0142	T
171	0.1055	0.0167	17	7240391	C	T	ACAP1	rs61759532	0.0988	T
172	0.1256	0.0198	12	53585859	C	T	ITGB7	rs11170466	0.0643	T
173	0.097	0.0117	1	212909744	A	G	BATF3	rs11800642	0.1877	G
174	0.4027	0.0669	6	28699935	A	C	SCAND3	rs143609442	0.0014	C
175	−1.1814	0.1967	6	31295836	T	C	HLA-B	rs115184619	0.001	C
176	0.0858	0.0106	2	242407746	A	G	FARP2	rs10933559	0.1352	G
177	0.5461	0.091	6	25399414	A	G	LRRC16A	rs182650062	0.0018	G
178	−0.1041	0.0147	21	45624551	C	T	AP001055.1	rs56178904	0.1647	T
179	0.0766	0.0104	11	35270854	G	T	SLC1A2	rs10768120	0.3486	T
180	0.1304	0.0172	3	45919992	G	A	CCR9	rs57319220	0.1072	A
181	0.0787	0.0092	2	191973563	A	G	STAT4	rs6752770	0.2939	G
182	0.6989	0.117	6	27481335	G	A	ZNF184	rs74404372	0.001	A

183	0.0966	0.0133	21	45735363	A	G	PFKL	rs59952509	0.2051	G
184	−0.6046	0.1015	6	28060620	G	A	ZNF165	rs149765808	0.0024	A
185	0.3959	0.0665	11	2155182	C	G	IGF2	rs113257255	0.0038	G
186	0.5999	0.1008	6	30309337	G	A	RPP21	rs190763129	0.0014	A
187	−0.4194	0.0706	6	28666711	G	A	SCAND3	rs115401958	0.0016	A
188	0.825	0.139	6	25822917	C	T	SLC17A1	rs186212005	0.0004	T
189	−0.0961	0.0112	17	44797919	C	T	NSF	rs199456	0.0795	T
190	−0.6051	0.1021	6	27155049	AAC	A	HIST1H2AH	rs551145084	0.002	–
191	−0.0755	0.0104	6	25410077	C	T	LRRC16A	rs4368803	0.2987	T
192	0.1082	0.0178	2	242420422	C	G	FARP2	rs12988792	0.1352	G
193	−0.0814	0.0142	8	59872177	A	G	TOX	rs1947178	0.3466	A
194	0.0881	0.0107	15	38900312	C	A	RASGRP1	rs17652674	0.1228	A
195	−0.0735	0.0092	7	50305863	T	G	IKZF1	rs4917014	0.2784	G
196	0.1702	0.0276	5	110566360	C	T	CAMK4	rs114378220	0.0262	T
197	−0.1056	0.0168	8	141616183	T	C	AGO2	rs3802214	0.2524	T
198	0.5186	0.0889	1	114834108	G	A	SYT6	rs141411272	0.0022	A
199	0.0831	0.0137	7	20454565	G	C	ITGB8	rs35386086	0.1426	C
200	−0.0687	0.0097	4	38383633	T	C	KLF3	rs10004996	0.398	C
201	0.8293	0.1433	6	27379085	C	T	ZNF391	rs531887565	0.0004	T
202	0.545	0.0943	6	29079152	C	T	OR2J3	rs117788472	0.0054	T
203	−0.1486	0.0241	12	9063252	A	G	PHC1	rs113748894	0.0284	G
204	0.3837	0.0666	6	32462871	C	T	HLA-DRB5	rs573175256	0.0024	T
205	0.4778	0.0829	1	113329197	C	T	FAM19A3	rs185536957	0.0012	T
206	−0.0764	0.0099	1	117280696	C	T	CD2	rs798000	0.2426	C
207	0.5594	0.0972	1	114194164	G	C	PHTF1	rs186758851	0.0016	C
208	−1.0251	0.1784	6	32767188	C	T	HLA-DOB	rs35096774	0.0012	T
209	−0.2703	0.0457	6	35501016	C	T	TULP1	rs78086481	0.0256	T
210	0.8352	0.1457	6	28148718	A	G	ZKSCAN8	rs181861261	0.0006	G
211	0.3456	0.0604	6	33728651	A	G	IP6K3	rs12203746	0.0028	G
212	−0.1011	0.017	4	185302902	C	G	IRF2	rs12644686	0.3063	G
213	1.2293	0.2149	6	31802221	A	G	C6orf48	rs186867042	0.0012	G
214	−0.0907	0.0132	1	172779584	A	G	FASLG	rs12137048	0.0635	G
215	1.6691	0.2929	6	24044294	G	A	NRSN1	rs551378401	0.0002	A
216	0.0716	0.0092	14	90202764	C	T	RP11-944C7.1	rs10137250	0.4926	C
217	1.1959	0.2112	6	32726930	G	A	HLA-DQB2	rs34056220	0.0349	A
218	0.1036	0.0179	2	242406108	C	G	FARP2	rs115979345	0.1076	G
219	−0.0708	0.0092	17	46519923	T	C	SKAP1	rs7211780	0.4649	C
220	−0.1231	0.0223	1	36087661	C	A	PSMB2	rs574384	0.4792	A
221	0.0689	0.0088	17	38775150	C	T	SMARCE1	rs757411	0.3079	C
222	0.3139	0.0557	21	45714294	C	T	AIRE	rs74203920	0.0044	T
223	0.1147	0.0194	14	68967196	G	A	RAD51B	rs12590642	0.1899	A
224	0.3791	0.0674	6	34852882	CT	C	TAF11			
225	0.3475	0.0613	11	2182823	C	G	INS	rs61872713	0.0974	C
226	4.1884	0.7455	6	24197475	T	A	DCDC2	rs980500808		
227	−0.0812	0.0119	5	55442249	T	C	ANKRD55	rs10213692	0.1016	C
228	0.1003	0.0179	2	242278007	T	A	SEPTIN2	rs13018977	0.1212	A
229	0.084	0.0109	2	242261434	A	G	SEPTIN2	rs7570017	0.0775	G

(*continued*)

Table 12.1 (*Continued*)

No	beta	stdErr	chr	position	ref	alt	nearest_gene/locus	dbSNP	maf	Minor allele
230	−0.0796	0.0105	1	154437896	T	C	SHE	rs2229238	0.2031	T
231	5.1235	0.9162	6	9514914	C	T	OFCC1	rs1411407697		
232	−0.0761	0.0106	6	32900018	C	G	HLA-DMB	rs154977	0.2979	C
233	−0.5759	0.1031	6	32488663	T	C	HLA-DRB5	rs76312591	0.0763	C
234	−0.0843	0.0106	9	102368541	T	C	NR4A3	rs12237953	0.1701	C
235	−0.7913	0.1419	6	32405119	G	A	HLA-DRA	rs184635316	0.0006	A
236	−0.1001	0.0179	17	4300706	T	G	UBE2G1	rs9891059	0.2149	G
237	−0.8201	0.1471	11	2259363	C	T	ASCL2	rs564680007	0.0046	T
238	−0.0739	0.0128	2	12631916	T	C	TRIB2	rs10929817	0.2837	C
239	−0.2478	0.0445	6	28579589	G	C	SCAND3	rs11753996	0.0092	C
240	0.4503	0.0809	6	30652376	C	T	PPP1R18	rs199834022	0.0012	T
241	0.0818	0.0138	20	10482703	C	T	SLX4IP	rs998934	0.0707	T
242	0.3446	0.0621	6	26260695	G	A	HIST1H2BH	rs112252880	0.0046	A
243	−0.0726	0.0129	1	38398588	T	C	INPP5B	rs17465420	0.3562	C
244	0.1847	0.0338	11	60729294	G	T	SLC15A3	rs79538630	0.0507	T
245	−0.0838	0.0117	8	11744219	T	G	CTSB	rs1692791	0.3165	G
246	−0.0811	0.0135	5	86257546	C	T	AC008394.1	rs10942481	0.3381	T
247	0.0987	0.0178	2	242278547	G	A	SEPTIN2	rs28648882	0.1214	A
248	0.0687	0.0116	19	499978	G	A	MADCAM1	rs12982646	0.1573	A
249	−0.445	0.0805	6	28765646	AC	A	TRIM27	rs531909398	0.0018	–
250	−0.0833	0.0128	19	18520231	A	G	SSBP4	rs11086110	0.1799	G
251	0.746	0.1358	6	30006713	A	T	ZNRD1	rs190234164	0.0008	T
252	−0.314	0.0572	6	27180474	A	C	PRSS16	rs62401084	0.007	C
253	0.4126	0.0753	11	2903060	G	A	CDKN1C	rs140215710	0.0038	A
254	0.0843	0.0153	2	242410421	C	G	FARP2	rs6737152	0.2556	G
255	−0.2555	0.0468	11	2291195	T	C	ASCL2	rs376558492	0.0082	C
256	−0.3949	0.0723	6	27996825	G	A	ZNF165	rs142392386	0.0018	A
257	0.0885	0.0134	11	118233078	A	G	UBE4A	rs3782045	0.2985	G

in subsequent studies. The greatest success in linkage studies relates to the discovery of variants in *TCF7L2* associated with type 2 diabetes. The DeCode team observed a rather modest linkage at a 10.5 Mb region on chromosome 10q, but decided to pursue and fine map it, thereby identifying the variant that shows the strongest association with type 2 diabetes, an intronic variant (rs7903146) in the *TCF7L2* gene contributing to, but not fully explaining, the original linkage [71–73]. This association has since been confirmed in African, Asian, and European populations, rendering it the most consistently replicated genetic association with type 2 diabetes, conferring a relative risk of ~1.4 [74].

Candidate genes for type 2 diabetes

The first candidate gene reproducibly associated with type 2 diabetes was *PPARG*, encoding the nuclear receptor PPAR-γ [75]. The PPAR-γ receptor is a molecular target for thiazolidinediones, a class of insulin-sensitizing drugs used to treat type 2 diabetes, making it a compelling candidate gene. The transcript expressed in adipose tissue has an extra exon B and a substitution of a proline for alanine at position 12 of this protein, which is seen in ~15% of the European population. This variant is associated with increased transcriptional activity, increased insulin sensitivity, and protection against type 2 diabetes [75].

Type 2 diabetes risk variants in *KCJN11* were also discovered through candidate association studies [76,77]. *KCNJ11* codes for four subunits of the ATP-sensitive potassium (K-ATP) channel, the other four coded by another gene (*ABCC8*). The E23K polymorphisms in *KCNJ11* and P12A in *PPARG* putatively acted in an additive manner to increase the risk of type 2 diabetes [78]. In pancreatic β cells, ATP–potassium channels are crucial for the regulation of glucose-stimulated insulin secretion and are the target for the sulfonylureas, which are oral hypoglycaemic agents widely used in the treatment of type 2 diabetes, and for diazoxide, a potassium channel opener. Activating mutations in this gene also caused neonatal diabetes. Additionally, loss-of-function mutations in *KCNJ11* and *ABCC8* caused hyperinsulinemia in infancy [79].

Genome-wide association studies identify common variants associated with type 2 diabetes

The development of new genotyping technologies and the realization that we inherit stretches of the genome together as haplotypes facilitated cataloguing of common variants (e.g., HAPMAP, 1000 Genomes, TOPMED) and allowed for new possibilities for applying unbiased global approaches to screen millions of common variants for association with complex diseases. Several GWAS for diabetes were published in 2007, termed Breakthrough of the Year by *Science* magazine. The first was a GWAS on early-onset type 2 diabetes reporting two new diabetes loci, *HHEX* and *SLC30A8* [80]. The ultimate proof of the value of GWAS for type 2 diabetes came from three studies published back to back in *Science* in 2007; for the first time in the genetics of type 2 diabetes, three different studies reported the same top findings [81–83].

The first wave of GWAS was followed by a second wave combining existing or new GWAS into meta-analyses of >50 000 individuals [12]. A prerequisite for this was that many research groups could work together in consortia like DIAGRAM (DIAbetes Genetics Replication and Meta-analysis Consortium) and MAGIC (Meta-Analyses of Glucose-and Insulin-related traits Consortium). GWAS do not inevitably lead to identification of a gene or genes in a given locus associated with disease. Since the most strongly associated SNPs are often only markers for the functional variant responsible for the observed genetic effect and most associated regions harbour several genes, additional fine mapping of the loci in even larger sample sets is often necessary. To do this cost-efficiently a custom-designed chip, the so-called CardioMetabochip (Illumina, San Diego, CA, USA), has been developed for metabolic and cardiovascular gene mapping. This chip contains ~200 000 polymorphisms selected to cover association signals from a wide range of metabolic disorders (type 2 diabetes, lipid disorders, obesity, and cardiovascular disease) and was designed to perform both deep replication of major disease signals and fine mapping of established loci. Meta-analysis of previous GWAS by the DIAGRAM consortium with an additional 22 669 individuals with type 2 diabetes and 58 119 controls genotyped using the CardioMetabochip has recently added another eight new loci associated with type 2 diabetes in the European population and two novel loci not previously reported in populations of European descent [84].

Recently, GWAS and meta-analysis studies have also been performed in non-European cohorts, adding several new loci to the list of genome-wide significant associations [85–95]. Interestingly, most associations found in one ethnic group also show some evidence of association in populations with other ethnicities. GWAS have now provided ~1102 variants for type 2 diabetes mapping to >660 loci (Table 12.2), as well as numerous loci for glucose- or insulin-related traits (Table 12.3, Figure 12.2), and more are likely to come.

Most studies have been limited to SNPs, leaving structural polymorphisms relatively unexplored. However, since common structural variants are likely to be tagged by surrounding SNPs, they are unlikely to explain a large proportion of missing heritability. A recent study identified a common copy number variation, CNVR5583.1 (*TSPAN8*), as associated with type 2 diabetes [102]. This association could be convincingly replicated by previously typed SNPs that tag the copy number variation [103].

Rare variants with stronger effects are often rare

Rare variants are more recent and therefore more likely to be those that arose recently in an extended pedigree. Of course, natural selection removes the more deleterious variants before they reach a high frequency and so risk alleles for diseases should be enriched at lower frequencies. The idea that there are unique rare variant combinations in families that play a role in disease aetiology is referred to as *clan genomics* [52]. Current data suggest that combined effects of rare and common variants contribute in varying degrees to disease causation, not least linkage, and that rare alleles may, in fact, explain the majority of heritability [104]. Next-generation sequencing provides even denser coverage of genetic variation, rendering detection of causal rare variants more feasible. Whole-genome sequencing of 2630 Icelanders and imputation into 11 114 Icelandic cases and 267 140 controls followed by testing in Danish and Iranian samples revealed variants in *PAM* and *PDX1* in the risk of type 2 diabetes [105] (Table 12.4). Array-based genotyping and exome sequencing on a small founder population

Table 12.2 Genetic loci associated with risk of type 2 diabetes.

slno	Nearest gene (*=BMI adjusted)	Index variant	Chromosome	Position (Build 37 bp)	Risk allele	Other allele	RAF (%)	OR (95% CI)/ beta (se)#	Reference
1	*PAM*	rs78408340	5	102338739	G	C	0.83	1.47 (1.37–1.59)	[93]
2	*DENND2C*	rs184660829	1	115144899	C	T	0.02	8.05 (3.86–16.8)	[93]
3	*KIF2B*	rs569511541	17	52140805	G	A	0.02	7.63 (3.78–15.4)	[93]
4	*RMST*	rs759111467	12	97562756	A	G	0.03	3.07 (1.94–4.85)	[93]
5	*LTK*	rs543786825	15	42201410	T	C	0.04	3.15 (1.93–5.15)	[93]
6	*SLC25A51P1*	rs555402748	6	67387490	T	C	0.04	3.67 (2.30–5.86)	[93]
7	*FARSA*	rs755734872	19	12938471	T	C	0.05	2.37 (1.62–3.46)	[93]
8	*TCF4*	rs76197067	18	52604955	G	A	0.05	2.68 (1.74–4.12)	[93]
9	*GIPR*	rs533172266	19	46351837	T	C	0.06	2.33 (1.63–3.33)	[93]
10	*RMST*	rs557027608	12	97779248	A	G	0.06	2.34 (1.69–3.24)	[93]
11	*DDX18*	rs562386202	2	118071061	G	A	0.06	3.20 (2.11–4.86)	[93]
12	*GPSM1*	9:139737088:G:A	9	139737088	A	G	0.07	2.74 (1.76–4.25)	[93]
13	*BPTF*	rs558308082	17	65820153	C	G	0.08	2.04 (1.49–2.77)	[93]
14	*QSER1*	rs528122639	11	33091735	A	G	0.09	2.09 (1.59–2.76)	[93]
15	*KCNJ11*	rs67254669	11	17470143	G	A	0.11	1.89 (1.52–2.35)	[93]
16	*LYPLAL1*	rs553014999	1	219584164	C	T	0.13	1.90 (1.43–2.51)	[93]
17	*FAM13A*	rs576406049	4	89857291	T	C	0.13	1.65 (1.35–2.03)	[93]
18	*TOMM40/APOE*	rs745903616	19	44938870	A	G	0.13	1.61 (1.30–1.98)	[93]
19	*INS/IGF2*	rs571342427	11	2182519	C	T	0.15	1.68 (1.36–2.07)	[93]
20	*INSR*	rs75253922	19	7240848	C	T	0.19	1.05 (1.03–1.06)	[93]
21	*TMCC1*	rs559138871	3	129470067	T	C	0.2	1.49 (1.25–1.77)	[93]
22	*EYA2*	rs560716466	20	45317678	A	G	0.31	1.36 (1.19–1.56)	[93]
23	*SLCO6A1*	rs138337556	5	101232944	G	A	0.36	1.56 (1.34–1.81)	[93]
24	*TMEM127**	rs79046683	2	96913918	T	G	0.48	2.34 (1.73–3.16)	[93]
25	*INS/IGF2*	rs555759341	11	2151761	C	G	0.49	1.38 (1.23–1.55)	[93]
26	*TCF7L2*	rs140242150	10	114702962	A	G	0.5	1.36 (1.22–1.52)	[93]
27	*TCF7L2*	rs536643418	10	114699835	G	C	0.52	1.50 (1.30–1.73)	[93]
28	*NEUROG3*	rs549498088	10	71347311	T	C	0.6	1.56 (1.31–1.86)	[93]
29	*FAM57B*	rs199795270	16	30419384	C	G	0.65	1.25 (1.14–1.36)	[93]
30	*WDR72*	rs528350911	15	53747228	G	C	0.68	1.27 (1.17–1.38)	[93]
31	*HNF1A*	rs73224262	12	121882395	T	C	0.68	1.24 (1.14–1.34)	[93]
32	*CPQ*	rs149364428	8	97737741	A	G	0.01	1.27 (1.19–1.36)	[93]
33	*TCF7L2*	rs180988137	10	114751173	G	A	0.01	1.17 (1.09–1.25)	[93]
34	*SRGAP2D*	rs76251711	13	59184234	G	A	0.013	1.16 (1.09–1.23)	[93]
35	*FAM63A*	rs10305745	1	150786038	A	G	0.015	1.28 (1.15–1.42)	[93]
36	*PCGF3*	rs111827885	4	616608	C	T	0.016	1.18 (1.10–1.27)	[93]
37	*TM6SF2*	rs188247550	19	19396616	T	C	0.02	1.15 (1.08–1.22)	[93]
38	*IGF2BP3*	rs78840640	7	23434606	G	C	0.022	1.11 (1.06–1.16)	[93]
39	*PROX1*	rs114526150	1	214175531	G	T	0.023	1.12 (1.07–1.17)	[93]
40	*TP53INP1*	rs187936726	8	96092422	G	A	0.024	1.11 (1.06–1.16)	[93]
41	*ETS1*	rs112595469	11	128583975	T	C	0.028	1.10 (1.05–1.14)	[93]
42	*ANKH*	rs76549217	5	14768766	T	C	0.03	1.14 (1.10–1.19)	[93]
43	*HNF1A*	rs1800574	12	121416864	T	C	0.03	1.14 (1.10–1.19)	[93]
44	*UBE2E2*	rs17013314	3	23510044	G	A	0.031	1.11 (1.07–1.15)	[93]
45	*MRPS30*	rs62368490	5	44534364	T	C	0.031	1.10 (1.06–1.14)	[93]

46	*ITGA1*	rs62357230	5	52315682	A	G	0.034	1.09 (1.05–1.13)	[93]
47	*CDKN2A/B*	rs76011118	9	22133773	A	G	0.034	1.11 (1.07–1.15)	[93]
48	*PROX1*	rs79687284	1	214150821	C	G	0.035	1.16 (1.12–1.21)	[93]
49	*HNF4A*	rs1800961	20	43042364	T	C	0.035	1.18 (1.15–1.23)	[93]
50	*TCF12*	rs117483894	15	57456802	G	A	0.037	1.10 (1.06–1.13)	[93]
51	*PTPRS*	rs116953931	19	5224998	A	G	0.037	1.08 (1.04–1.12)	[93]
52	*ANKH*	rs17250977	5	14753745	G	A	0.038	1.12 (1.09–1.16)	[93]
53	*ANK1*	rs148766658	8	41552046	C	T	0.038	1.09 (1.05–1.13)	[93]
54	*HMGA1**	rs77136196	6	34247047	T	C	0.042	1.11 (1.07–1.16)	[93]
55	*HNF4A*	rs76811102	20	42905415	T	C	0.042	1.09 (1.06–1.13)	[93]
56	*NEUROG3*	rs41277236	10	71332301	T	C	0.043	1.09 (1.05–1.12)	[93]
57	*HNF1A*	rs28638142	12	121501461	A	C	0.044	1.08 (1.04–1.11)	[93]
58	*PCGF3*	rs1531583	4	744972	T	G	0.046	1.13 (1.09–1.16)	[93]
59	*GRB14/COBLL1*	rs13024606	2	165573194	T	C	0.047	1.09 (1.06–1.13)	[93]
60	*PIM3*	rs112915006	22	50604696	G	A	0.051	1.08 (1.05–1.11)	[93]
61	*FTO*	rs78020297	16	53758720	A	G	0.052	1.09 (1.06–1.12)	[93]
62	*FBXL13*	rs56376556	7	102038318	T	C	0.053	1.08 (1.04–1.11)	[93]
63	*ST6GAL1*	rs7645517	3	186675277	A	G	0.058	1.08 (1.05–1.11)	[93]
64	*NF1*	rs71372253	17	29413019	C	T	0.064	1.08 (1.05–1.10)	[93]
65	*HNF1A*	rs11065299	12	121297815	A	G	0.075	1.06 (1.04–1.09)	[93]
66	*TM6SF2*	rs8107974	19	19388500	T	A	0.077	1.10 (1.07–1.12)	[93]
67	*GNAS*	rs862016	20	57551099	G	A	0.078	1.07 (1.04–1.09)	[93]
68	*RELN*	rs62482405	7	102987583	G	T	0.082	1.05 (1.03–1.08)	[93]
69	*USP46*	rs114447556	4	53207093	T	C	0.084	1.06 (1.03–1.08)	[93]
70	*BPTF*	rs11657492	17	65648427	G	T	0.1	1.06 (1.04–1.08)	[93]
71	*KIF9*	rs75423501	3	47242923	G	A	0.101	1.05 (1.03–1.08)	[93]
72	*KCNQ1*	rs231349	11	2672821	T	C	0.102	1.07 (1.05–1.10)	[93]
73	*HMGA2*	rs2258238	12	66221060	T	A	0.104	1.10 (1.08–1.13)	[93]
74	*HNF4A*	rs4810426	20	43001721	T	C	0.106	1.09 (1.07–1.12)	[93]
75	*NKX2.2*	rs13041756	20	21466795	C	T	0.107	1.06 (1.04–1.08)	[93]
76	*NOTCH2*	rs1493694	1	120526982	T	C	0.109	1.09 (1.07–1.11)	[93]
77	*COMMD9*	rs62080313	18	36278709	C	T	0.123	1.06 (1.04–1.08)	[93]
78	*RASGRP1*	rs34715063	15	38873115	C	T	0.124	1.10 (1.07–1.12)	[93]
79	*ONECUT1*	rs2456530	15	53091553	T	C	0.127	1.06 (1.04–1.08)	[93]
80	*ACE*	rs60276348	17	62203304	T	C	0.14	1.05 (1.03–1.07)	[93]
81	*PTEN**	rs11202627	10	89769340	T	C	0.152	1.06 (1.04–1.08)	[93]
82	*PABPC1P2*	rs35999103	2	147861633	T	C	0.155	1.05 (1.03–1.07)	[93]
83	*ZZEF1*	rs1043246	17	3828086	G	C	0.157	1.05 (1.03–1.07)	[93]
84	*TCF4*	rs28719468	18	53452144	C	T	0.159	1.04 (1.02–1.06)	[93]
85	*QSER1*	rs7943101	11	32460873	T	C	0.161	1.04 (1.02–1.06)	[93]
86	*ITGA1*	rs3811978	5	52100489	G	A	0.167	1.06 (1.04–1.07)	[93]
87	*KL*	rs576674	13	33554302	G	A	0.169	1.05 (1.04–1.07)	[93]
88	*MHC*	rs601945	6	32573415	G	A	0.178	1.06 (1.04–1.08)	[93]
89	*CCND2*	rs11063028	12	4300172	C	T	0.18	1.06 (1.04–1.07)	[93]
90	*DGKB*	rs17168486	7	14898282	T	C	0.181	1.07 (1.06–1.09)	[93]
91	*PDHX*	rs286925	11	34642668	A	G	0.182	1.04 (1.02–1.06)	[93]
92	*BPTF*	rs61676547	17	65892507	C	G	0.192	1.06 (1.04–1.07)	[93]
93	*ANKRD55*	rs9687832	5	55861595	A	G	0.198	1.08 (1.06–1.10)	[93]

(*continued*)

Table 12.2 (*Continued*)

slno	Nearest gene (*=BMI adjusted)	Index variant	Chromosome	Position (Build 37 bp)	Risk allele	Other allele	RAF (%)	OR (95% CI)/ beta (se)#	Reference
94	*MACF1*	rs3768321	1	40035928	T	G	0.2	1.09 (1.07–1.10)	[93]
95	*MAP3K11*	rs1783541	11	65294799	T	C	0.204	1.06 (1.05–1.08)	[93]
96	*UHRF1*	rs7249758	19	4948862	A	G	0.204	1.05 (1.03–1.07)	[93]
97	*EBF1**	rs3934712	5	157928196	C	T	0.206	1.05 (1.03–1.07)	[93]
98	*ETS1*	rs67232546	11	128398938	T	C	0.207	1.06 (1.04–1.07)	[93]
99	*CCND2*	rs4238013	12	4376089	C	T	0.209	1.06 (1.04–1.07)	[93]
100	*NRXN3*	rs17836088	14	79932041	C	G	0.217	1.06 (1.04–1.08)	[93]
101	*CLUAP1*	rs3751837	16	3583173	T	C	0.22	1.04 (1.03–1.06)	[93]
102	*ARL15*	rs62370480	5	52774510	A	G	0.22	1.04 (1.02–1.05)	[93]
103	*HNF1B*	rs10962	17	36046451	C	G	0.226	1.05 (1.03–1.07)	[93]
104	*SLC7A7*	rs17122772	14	23288935	G	C	0.228	1.04 (1.03–1.06)	[93]
105	*MC4R*	rs523288	18	57848369	T	A	0.238	1.05 (1.04–1.07)	[93]
106	*TCEA2**	rs59944054	20	62693175	A	G	0.238	1.06 (1.04–1.08)	[93]
107	*IGF2BP2*	rs150111048	3	185514421	G	A	0.239	1.12 (1.07–1.16)	[93]
108	*RASGRP1*	rs8032939	15	38834033	C	T	0.246	1.06 (1.04–1.07)	[93]
109	*KCNQ1*	rs234853	11	2850828	G	A	0.248	1.08 (1.06–1.10)	[93]
110	*ITPR2*	rs718314	12	26453283	G	A	0.253	1.05 (1.03–1.06)	[93]
111	*CCND2*	rs3217860	12	4399050	G	A	0.258	1.05 (1.03–1.06)	[93]
112	*RASA1*	rs7719891	5	86577352	G	A	0.259	1.04 (1.03–1.06)	[93]
113	*ANKRD55*	rs96844	5	56196604	G	A	0.262	1.04 (1.03–1.05)	[93]
114	*AP3S2*	rs4932265	15	90423293	T	C	0.267	1.07 (1.05–1.08)	[93]
115	*CDKAL1*	rs7756992	6	20679709	G	A	0.274	1.15 (1.13–1.17)	[93]
116	*MLX*	rs34855406	17	40731411	C	G	0.277	1.05 (1.04–1.07)	[93]
117	*NEUROG3*	rs61850200	10	71321658	C	G	0.277	1.04 (1.02–1.05)	[93]
118	*PCDH17*	rs9537803	13	58366634	C	T	0.277	1.04 (1.03–1.06)	[93]
119	*HSD17B12*	rs1061810	11	43877934	A	C	0.288	1.05 (1.04–1.07)	[93]
120	*SLC35D3*	rs9494624	6	137300960	A	G	0.29	1.04 (1.03–1.06)	[93]
121	*PDHX*	rs2767036	11	34982148	C	A	0.291	1.04 (1.02–1.05)	[93]
122	*CEP68*	rs2052261	2	65355270	G	A	0.304	1.07 (1.04–1.09)	[93]
123	*ZBED3*	rs4457053	5	76424949	G	A	0.304	1.06 (1.05–1.08)	[93]
124	*ZZEF1*	rs1377807	17	4045440	C	G	0.312	1.05 (1.04–1.07)	[93]
125	*PURG*	rs10954772	8	30863938	T	C	0.314	1.04 (1.03–1.06)	[93]
126	*IGF2BP2*	rs6780171	3	185503456	A	T	0.314	1.14 (1.12–1.16)	[93]
127	*RAI1*	rs4925109	17	17661802	A	G	0.316	1.05 (1.03–1.06)	[93]
128	*MBNL1*	rs35497231	3	152433628	C	T	0.317	1.04 (1.02–1.05)	[93]
129	*USP46*	rs2102278	4	52818664	G	A	0.319	1.04 (1.02–1.05)	[93]
130	*GLP2R*	rs7222481	17	9785187	C	G	0.324	1.04 (1.03–1.05)	[93]
131	*KLF14*	rs2268382	7	130027037	C	A	0.327	1.03 (1.02–1.04)	[93]
132	*GPSM1*	rs11793035	9	139507212	C	T	0.331	1.04 (1.02–1.05)	[93]
133	*METTL15**	rs4923543	11	28534898	A	G	0.332	1.04 (1.03–1.06)	[93]
134	*SCD5*	rs12642790	4	83578271	A	G	0.338	1.04 (1.03–1.06)	[93]
135	*GLIS3*	rs10974438	9	4291928	C	A	0.357	1.05 (1.04–1.07)	[93]
136	*LTK*	rs11070332	15	41809205	A	G	0.358	1.05 (1.04–1.06)	[93]
137	*ATP2A1*	rs8046545	16	28915217	G	A	0.359	1.04 (1.02–1.05)	[93]
138	*PRC1*	rs12910825	15	91511260	G	A	0.361	1.05 (1.04–1.07)	[93]

139	*KCNQ1*	rs445084	11	2908754	G	A	0.361	1.03 (1.02–1.05)	[93]
140	*KCNJ11*	rs5213	11	17408404	C	T	0.362	1.07 (1.06–1.09)	[93]
141	*PCGF3*	rs35654957	4	1010077	C	T	0.367	1.03 (1.02–1.05)	[93]
142	*BCAR1*	rs3115960	16	75516534	G	C	0.37	1.03 (1.02–1.05)	[93]
143	*BOP1*	rs4977213	8	145507304	C	T	0.375	1.05 (1.04–1.07)	[93]
144	*MIR3668**	rs2982521	6	139835329	A	T	0.38	1.05 (1.03–1.06)	[93]
145	*MAP2K7*	rs4804833	19	7970635	A	G	0.39	1.05 (1.03–1.06)	[93]
146	*BNIPL*	rs6545714	2	59307725	G	A	0.392	1.04 (1.02–1.05)	[93]
147	*HAUS6*	rs7022807	9	19067833	G	A	0.401	1.04 (1.03–1.05)	[93]
148	*ANKRD55*	rs2431115	5	55848669	A	G	0.402	1.04 (1.03–1.06)	[93]
149	*RREB1*	rs112498319	6	7035734	C	A	0.409	1.03 (1.02–1.05)	[93]
150	*CELF1*	rs7124681	11	47529947	A	C	0.41	1.04 (1.03–1.05)	[93]
151	*FOCAD*	rs7867635	9	20241069	C	T	0.412	1.04 (1.02–1.05)	[93]
152	*GIPR*	rs2238689	19	46178661	C	T	0.418	1.04 (1.03–1.05)	[93]
153	*THADA*	rs28525376	2	43207872	G	T	0.422	1.03 (1.02–1.04)	[93]
154	*PPARG*	rs17819328	3	12489342	G	T	0.425	1.06 (1.04–1.07)	[93]
155	*KCNQ1*	rs2237895	11	2857194	C	A	0.426	1.12 (1.11–1.14)	[93]
156	*INS/IGF2*	rs12802972	11	1704596	A	G	0.428	1.03 (1.02–1.05)	[93]
157	*ATP1B2**	rs1641523	17	7549681	C	T	0.428	1.05 (1.04–1.07)	[93]
158	*CDKN2A/B*	rs10757283	9	22134172	T	C	0.43	1.11 (1.09–1.13)	[93]
159	*RELN*	rs39328	7	103444978	T	C	0.433	1.04 (1.02–1.05)	[93]
160	*DSTYK*	rs12048743	1	205114873	G	C	0.442	1.04 (1.03–1.05)	[93]
161	*PABPC4L*	rs1296328	4	137083193	A	C	0.446	1.04 (1.02–1.05)	[93]
162	*CRY2*	rs7115753	11	45912013	A	G	0.449	1.04 (1.03–1.05)	[93]
163	*BCL11A*	rs243024	2	60583665	A	G	0.46	1.06 (1.05–1.07)	[93]
164	*SLC12A8*	rs649961	3	124926637	T	C	0.465	1.04 (1.03–1.05)	[93]
165	*SLC9B1*	rs1580278	4	104140848	C	A	0.473	1.04 (1.03–1.05)	[93]
166	*AKAP6*	rs17522122	14	33302882	T	G	0.474	1.04 (1.03–1.05)	[93]
167	*TCF7L2*	rs7918400	10	114703136	T	C	0.476	1.06 (1.04–1.07)	[93]
168	*TP53INP1*	rs10097617	8	95961626	T	C	0.485	1.04 (1.03–1.06)	[93]
169	*BCL2A*	rs10469140	18	60668270	G	A	0.485	1.03 (1.02–1.04)	[93]
170	*VEGFA*	rs11967262	6	43760327	G	C	0.486	1.04 (1.03–1.05)	[93]
171	*HMGA2*	rs1042725	12	66358347	T	C	0.49	1.05 (1.03–1.06)	[93]
172	*GLIS3*	rs510807	9	3965689	A	C	0.491	1.03 (1.02–1.04)	[93]
173	*SRGAP2*	rs9430095	1	206593900	C	G	0.494	1.04 (1.02–1.05)	[93]
174	*FAM13A*	rs1903002	4	89740894	G	C	0.501	1.04 (1.02–1.05)	[93]
175	*THADA*	rs6708643	2	43430440	A	G	0.501	1.04 (1.02–1.05)	[93]
176	*JAZF1*	rs1708302	7	28198677	C	T	0.512	1.10 (1.08–1.11)	[93]
177	*SLC22A3*	rs474513	6	160770312	A	G	0.517	1.04 (1.03–1.05)	[93]
178	*GNAS*	rs6070625	20	57394628	G	C	0.517	1.05 (1.04–1.06)	[93]
179	*MSRA*	rs17689007	8	9974824	G	A	0.533	1.04 (1.03–1.05)	[93]
180	*ZMIZ1*	rs703972	10	80952826	G	C	0.533	1.07 (1.06–1.09)	[93]
181	*TRHR*	rs12680028	8	110123183	C	G	0.534	1.04 (1.02–1.05)	[93]
182	*CEBPB*	rs11699802	20	48832135	C	T	0.536	1.04 (1.03–1.06)	[93]
183	*DGKB*	rs10228066	7	15063569	T	C	0.537	1.07 (1.06–1.09)	[93]
184	*BOP1*	rs12719778	8	145879883	T	C	0.538	1.04 (1.03–1.05)	[93]
185	*USP44*	rs2197973	12	95928560	T	C	0.538	1.04 (1.02–1.05)	[93]
186	*FTO*	rs4281707	16	53501946	G	A	0.544	1.04 (1.03–1.05)	[93]

(*continued*)

Table 12.2 (*Continued*)

slno	Nearest gene (*=BMI adjusted)	Index variant	Chromosome	Position (Build 37 bp)	Risk allele	Other allele	RAF (%)	OR (95% CI)/ beta (se)#	Reference
187	*ANK1*	rs4736819	8	41509915	T	C	0.554	1.04 (1.02–1.05)	[93]
188	*C2CD4A/B*	rs8037894	15	62394264	G	C	0.566	1.05 (1.03–1.06)	[93]
189	*TSPAN8/LGR5*	rs1796330	12	71522953	G	C	0.571	1.05 (1.04–1.06)	[93]
190	*MTND2P8*	rs11137820	9	81359113	C	G	0.575	1.04 (1.02–1.05)	[93]
191	*ZZEF1*	rs3826482	17	3860356	A	T	0.576	1.03 (1.02–1.05)	[93]
192	*HHEX/IDE*	rs7078559	10	93924663	T	C	0.578	1.03 (1.02–1.05)	[93]
193	*GRB14/COBLL1*	rs10195252	2	165513091	T	C	0.586	1.07 (1.06–1.08)	[93]
194	*HHEX/IDE*	rs1112718	10	94479107	A	G	0.598	1.06 (1.03–1.08)	[93]
195	*CEP68*	rs2028150	2	65655012	C	G	0.598	1.05 (1.03–1.06)	[93]
196	*MBNL1*	rs13065698	3	152086533	A	G	0.6	1.05 (1.03–1.06)	[93]
197	*ZNF664**	rs825452	12	124509177	A	G	0.603	1.04 (1.02–1.05)	[93]
198	*IRS2*	rs7987740	13	109947213	T	C	0.609	1.04 (1.02–1.05)	[93]
199	*BNIPL*	rs10193538	2	58981064	T	G	0.61	1.04 (1.02–1.05)	[93]
200	*IGF2BP3*	rs4279506	7	23512896	G	C	0.61	1.06 (1.04–1.08)	[93]
201	*IGF2BP2*	rs11717959	3	185541213	G	T	0.621	1.04 (1.02–1.06)	[93]
202	*KIF9*	rs11926707	3	46925539	C	T	0.626	1.27 (1.17–1.38)	[93]
203	*CDKN2A/B*	rs1412830	9	22043612	C	T	0.628	1.04 (1.02–1.05)	[93]
204	*DGKB*	rs2908334	7	15206239	T	C	0.631	1.03 (1.02–1.04)	[93]
205	*GNG4*	rs291367	1	235690800	G	A	0.632	1.04 (1.03–1.06)	[93]
206	*CEP68*	rs2249105	2	65287896	A	G	0.634	1.10 (1.08–1.13)	[93]
207	*IRS1*	rs2972144	2	227101411	G	A	0.639	1.10 (1.08–1.11)	[93]
208	*TP53INP1*	rs11786992	8	95685147	A	C	0.644	1.03 (1.02–1.04)	[93]
209	*TFAP2B*	rs2465043	6	51180765	G	A	0.644	1.03 (1.02–1.04)	[93]
210	*DMGDH*	rs1316776	5	78430607	C	A	0.648	1.05 (1.03–1.06)	[93]
211	*MARK3*	rs62007683	14	103894071	G	T	0.653	1.04 (1.02–1.05)	[93]
212	*RALY*	rs2268078	20	32596704	A	G	0.657	1.04 (1.03–1.06)	[93]
213	*CDKN2A/B*	rs1333052	9	22157908	A	C	0.66	1.03 (1.02–1.05)	[93]
214	*INS/IGF2*	rs11042596	11	2118860	G	T	0.665	1.04 (1.03–1.05)	[93]
215	*ZNF664**	rs7978610	12	124468572	G	C	0.666	1.27 (1.17–1.38)	[93]
216	*IRS2*	rs4771648	13	110431626	G	A	0.669	1.04 (1.02–1.05)	[93]
217	*MNX1*	rs6459733	7	156930550	G	C	0.673	1.06 (1.05–1.07)	[93]
218	*BEND3*	rs4946812	6	107431688	G	A	0.674	1.04 (1.03–1.05)	[93]
219	*RBM6*	rs4688760	3	49980596	T	C	0.684	1.04 (1.03–1.06)	[93]
220	*SLC30A8*	rs3802177	8	118185025	G	A	0.685	1.11 (1.10–1.13)	[93]
221	*HMGA1**	rs2233632	6	34524698	T	C	0.688	1.04 (1.03–1.06)	[93]
222	*KCNQ1*	rs2283220	11	2755548	A	G	0.69	1.05 (1.03–1.06)	[93]
223	*ARL15*	rs702634	5	53271420	A	G	0.69	1.05 (1.04–1.07)	[93]
224	*ARL15*	rs279744	5	53412620	C	A	0.691	1.04 (1.03–1.05)	[93]
225	*NEUROG3*	rs2642588	10	71466578	G	T	0.702	1.05 (1.04–1.07)	[93]
226	*PHF15*	rs244665	5	133414622	A	G	0.703	1.03 (1.02–1.05)	[93]
227	*ADAMTS9*	rs9860730	3	64701146	A	G	0.704	1.06 (1.04–1.07)	[93]
228	*TMEM154*	rs7669833	4	153513369	T	A	0.705	1.06 (1.04–1.07)	[93]
229	*MTNR1B*	rs57235767	11	93013531	C	T	0.706	1.04 (1.03–1.06)	[93]
230	*WFS1*	rs1801212	4	6302519	A	G	0.709	1.05 (1.03–1.07)	[93]
231	*SRGAP2D*	rs9563615	13	59077406	A	T	0.71	1.05 (1.03–1.06)	[93]
232	*SLC2A2*	rs9873618	3	170733076	G	A	0.71	1.07 (1.05–1.08)	[93]

233	*RBMS1*	rs3772071	2	161135544	T	C	0.714	1.05 (1.03–1.06)	[93]
234	*HMG20A*	rs1005752	15	77818128	A	C	0.715	1.08 (1.07–1.10)	[93]
235	*LCORL*	rs12640250	4	17792869	C	A	0.715	1.04 (1.03–1.05)	[93]
236	*TCF7L2*	rs34855922	10	114871594	A	G	0.716	1.05 (1.04–1.07)	[93]
237	*SOGA3*	rs2800733	6	127416930	A	G	0.717	1.05 (1.03–1.06)	[93]
238	*EP300*	rs5758223	22	41489920	A	G	0.717	1.04 (1.03–1.05)	[93]
239	*SPRY2*	rs1359790	13	80717156	G	A	0.72	1.09 (1.07–1.10)	[93]
240	*EYA2*	rs6063048	20	45598564	G	A	0.725	1.05 (1.03–1.06)	[93]
241	*GLI2*	rs11688682	2	121347612	G	C	0.728	1.05 (1.03–1.06)	[93]
242	*DTNB*	rs17802463	2	25643221	G	T	0.731	1.04 (1.03–1.05)	[93]
243	*ZNF169*	rs55653563	9	97001682	A	C	0.732	1.04 (1.03–1.06)	[93]
244	*HMGB1*	rs11842871	13	31042452	G	T	0.735	1.04 (1.03–1.06)	[93]
245	*MIR3668**	rs616279	6	140249466	A	G	0.738	1.04 (1.03–1.06)	[93]
246	*WDR7*	rs17684074	18	54675384	G	C	0.74	1.04 (1.03–1.06)	[93]
247	*CLEC14A*	rs8017808	14	38848419	G	T	0.743	1.04 (1.03–1.06)	[93]
248	*GPSM1*	rs28505901	9	139241030	G	A	0.752	1.09 (1.07–1.11)	[93]
249	*ACE*	rs2727301	17	61965043	T	C	0.754	1.04 (1.02–1.05)	[93]
250	*PTPN9*	rs13737	15	75932129	G	T	0.759	1.05 (1.03–1.06)	[93]
251	*IGF2BP2*	rs1516728	3	185829891	A	T	0.759	1.03 (1.02–1.05)	[93]
252	*KCNQ1*	rs4930091	11	2372356	C	T	0.759	1.04 (1.02–1.05)	[93]
253	*MPHOSPH9*	rs4148856	12	123450765	C	G	0.781	1.05 (1.03–1.07)	[93]
254	*XKR6*	rs57327348	8	10808687	A	T	0.782	1.04 (1.02–1.06)	[93]
255	*UBE2E2*	rs35352848	3	23455582	T	C	0.788	1.07 (1.05–1.09)	[93]
256	*ZMIZ1*	rs1317617	10	81096589	G	A	0.798	1.04 (1.02–1.06)	[93]
257	*RREB1*	rs9505097	6	7255650	C	T	0.799	1.05 (1.03–1.07)	[93]
258	*CCND2*	rs10848958	12	4031104	C	T	0.804	1.04 (1.03–1.06)	[93]
259	*KLHDC5*	rs10842994	12	27965150	C	T	0.805	1.08 (1.06–1.09)	[93]
260	*FBXL13*	rs11496066	7	102486254	T	C	0.818	1.08 (1.05–1.11)	[93]
261	*PCDH17*	rs9569864	13	58965435	C	T	0.825	1.05 (1.03–1.06)	[93]
262	*CDKN2A/B*	rs10811660	9	22134068	G	A	0.828	1.27 (1.24–1.29)	[93]
263	*KSR2*	rs12578639	12	118489636	A	T	0.828	1.04 (1.02–1.06)	[93]
264	*TMEM18*	rs35913461	2	653575	C	T	0.829	1.06 (1.04–1.08)	[93]
265	*GRP*	rs9957145	18	56876228	G	A	0.829	1.05 (1.03–1.07)	[93]
266	*GCK*	rs116913033	7	44365549	C	T	0.83	1.04 (1.02–1.06)	[93]
267	*CCND1*	rs61881115	11	68997225	G	A	0.838	1.05 (1.03–1.06)	[93]
268	*FOCAD*	rs7847880	9	20662703	C	T	0.843	1.04 (1.03–1.06)	[93]
269	*PSMD6*	rs3774723	3	63962339	G	A	0.844	1.07 (1.05–1.09)	[93]
270	*GLI2*	rs11688931	2	121318166	C	G	0.849	1.04 (1.02–1.06)	[93]
271	*TCF7L2*	rs78025551	10	114757956	C	G	0.851	1.05 (1.03–1.07)	[93]
272	*ETS1*	rs10893829	11	128042575	T	C	0.853	1.06 (1.04–1.08)	[93]
273	*EGFEM1P*	rs7629630	3	168218841	A	T	0.857	1.05 (1.03–1.07)	[93]
274	*ACSL1*	rs58730668	4	185717759	T	C	0.858	1.07 (1.05–1.09)	[93]
275	*HNF1B*	rs2189301	17	36063685	G	A	0.872	1.05 (1.03–1.08)	[93]
276	*PPARG*	rs11709077	3	12336507	G	A	0.877	1.14 (1.11–1.16)	[93]
277	*FAF1*	rs58432198	1	51256091	C	T	0.881	1.07 (1.05–1.09)	[93]
278	*GPSM1*	rs78403475	9	139235606	G	C	0.896	1.06 (1.03–1.08)	[93]
279	*TMCC1*	rs9828772	3	129333182	C	G	0.898	1.06 (1.04–1.08)	[93]
280	*ANKH*	rs3845281	5	14610134	G	A	0.904	1.08 (1.06–1.10)	[93]

(*continued*)

Table 12.2 (*Continued*)

slno	Nearest gene (*=BMI adjusted)	Index variant	Chromosome	Position (Build 37 bp)	Risk allele	Other allele	RAF (%)	OR (95% CI)/ beta (se)#	Reference
281	*THADA*	rs80147536	2	43698028	A	T	0.904	1.13 (1.11–1.16)	[93]
282	*YWHAH*	rs117001013	22	32348841	C	T	0.912	1.07 (1.04–1.09)	[93]
283	*CCND2*	rs3217792	12	4384696	C	T	0.913	1.12 (1.10–1.15)	[93]
284	*MTMR3/ASCC2*	rs6518681	22	30609554	G	A	0.914	1.09 (1.06–1.11)	[93]
285	*ATP1B2**	rs62059712	17	7740170	T	C	0.918	1.07 (1.04–1.10)	[93]
286	*BCAR1*	rs72802342	16	75234872	C	A	0.923	1.17 (1.14–1.20)	[93]
287	*SHQ1*	rs13085136	3	72865183	C	T	0.928	1.08 (1.05–1.10)	[93]
288	*TLE4*	rs17791513	9	81905590	A	G	0.932	1.10 (1.08–1.13)	[93]
289	*RMST*	rs77864822	12	97848775	A	G	0.932	1.08 (1.05–1.11)	[93]
290	*HNF4A*	rs11696357	20	43233649	A	G	0.934	1.06 (1.04–1.09)	[93]
291	*CYTIP*	rs13426680	2	158339550	A	G	0.937	1.09 (1.06–1.11)	[93]
292	*KCNQ1*	rs2283164	11	2579163	A	G	0.947	1.08 (1.05–1.12)	[93]
293	*TMEM18*	rs62107261	2	422144	T	C	0.954	1.12 (1.08–1.15)	[93]
294	*MBNL1*	rs74653713	3	152417881	C	A	0.957	1.10 (1.06–1.13)	[93]
295	*CDKN2A/B*	rs1575972	9	22301092	T	A	0.967	1.10 (1.06–1.14)	[93]
296	*GLI2*	rs66477705	2	121378852	T	C	0.967	1.09 (1.05–1.13)	[93]
297	*HNF1A*	rs73226260	12	121380541	G	A	0.967	1.13 (1.09–1.17)	[93]
298	*CCND1*	rs11820019	11	69448758	T	C	0.973	1.16 (1.11–1.20)	[93]
299	*MC4R*	rs74452128	18	58056566	C	A	0.976	1.15 (1.10–1.20)	[93]
300	*SLC30A8*	rs80244329	8	118404672	G	A	0.978	1.11 (1.06–1.17)	[93]
301	*TCF7L2*	rs184509201	10	114740337	C	G	0.982	1.21 (1.15–1.27)	[93]
302	*KCNQ1*	rs80102379	11	2634177	G	T	0.982	1.15 (1.09–1.21)	[93]
303	*GLIS3*	rs79103584	9	4243045	T	A	0.986	1.14 (1.08–1.21)	[93]
304	*ZNF169*	rs12236906	9	97497494	T	C	0.987	1.15 (1.08–1.22)	[93]
305	*HNF4A*	rs191830490	20	43023355	G	A	0.994	1.24 (1.13–1.36)	[93]
306	*PSMD6*	rs74368513	3	64460694	G	A	0.996	1.31 (1.16–1.47)	[93]
307	*KSR2*	rs34965774	12	118412373	A	G	0.14	1.06 (1.04–1.08)	[93,94]
308	*WDR11**	rs72631105	10	122915345	A	G	0.19	1.06 (1.04–1.08)	[93,94]
309	*PNPLA3*	rs738408	22	44324730	T	C	0.23	1.05 (1.03–1.07)	[93,94]
310	*GCK*	rs878521	7	44255643	A	G	0.24	1.06 (1.04–1.07)	[93,94]
311	*VEGFA*	rs6458354	6	43814190	C	T	0.29	1.05 (1.04–1.07)	[93,94]
312	*CMIP*	rs2925979	16	81534790	T	C	0.3	1.05 (1.04–1.07)	[93,94]
313	*ABO*	rs505922	9	136149229	C	T	0.33	1.05 (1.03–1.06)	[93,94]
314	*MRPS30*	rs6884702	5	44682589	G	A	0.39	1.04 (1.03–1.06)	[93,94]
315	*PHF15*	rs329122	5	133864599	A	G	0.43	1.04 (1.03–1.05)	[93,94]
316	*SMARCAD1*	rs6821438	4	95091911	A	G	0.53	1.04 (1.03–1.06)	[93,94]
317	*RFT1*	rs2581787	3	53127677	T	G	0.563	1.04 (1.02–1.05)	[93,94]
318	*NFAT5*	rs862320	16	69651866	C	T	0.58	1.04 (1.03–1.06)	[93,94]
319	*FARSA, FARSA-ZNF799*	rs3111316	19	13038415	A	G	0.589	1.05 (1.03–1.06)	[93,94]
320	*BCL6-LPP*	rs4686471	3	187740899	C	T	0.61	1.06 (1.05–1.08)	[93,94]
321	*POC5, HMGCR-POC5*	rs2307111	5	75003678	T	C	0.61	1.05 (1.04–1.07)	[93,94]
322	*ZC3H4*	rs3810291	19	47569003	A	G	0.67	1.05 (1.03–1.06)	[93,94]
323	*DLEU1*	rs963740	13	51096095	A	T	0.71	1.04 (1.03–1.05)	[93,94]
324	*ANKRD55*	rs465002	5	55808475	T	C	0.74	1.11 (1.09–1.12)	[93,94]
325	*TSHZ2*	rs34454109	20	51223594	A	T	0.77	1.04 (1.03–1.06)	[93,94]
326	*ITFG3*	rs6600191	16	295795	T	C	0.83	1.06 (1.05–1.08)	[93,94]

327	*CENTD2/ARAP1*	rs77464186	11	72460398	A	C	0.84	1.11 (1.09–1.13)	[93,94]
328	*ANKH*	rs6885132	5	14768092	C	G	0.9	1.07 (1.04–1.09)	[93,94]
329	*QSER1*	rs145678014	11	32927778	G	T	0.96	1.11 (1.07–1.14)	[93,94]
330	*PDE3B*	rs141521721	11	14763828	A	C	0.024	1.13 (1.08–1.17)	[93,94]
331	*PAM, SLCO6A1-PAM*	rs115505614	5	102422968	T	C	0.05	1.19 (1.15–1.22)	[93,94]
332	*SPG7*	rs12920022	16	89564055	A	T	0.158	1.05 (1.04–1.07)	[93,94]
333	*KLF14*	rs1562396	7	130457914	G	A	0.319	1.06 (1.05–1.08)	[93,94]
334	*FBRSL1*	rs12811407	12	133069698	A	G	0.331	1.05 (1.04–1.07)	[93,94]
335	*FAM57B*	rs11642430	16	30045789	G	C	0.399	1.04 (1.03–1.05)	[93,94]
336	*HNF1B*	rs10908278	17	36099952	T	A	0.481	1.08 (1.07–1.10)	[93,94]
337	*ITGA1*	rs17261179	5	51791225	T	C	0.517	1.04 (1.02–1.05)	[93,94]
338	*PEPD*	rs10406327	19	33890838	C	G	0.523	1.04 (1.02–1.05)	[93,94]
339	*GIPR, TOMM40-APOE-GIPR*	rs10406431	19	46157019	A	G	0.563	1.05 (1.04–1.06)	[93,94]
340	*HHEX/IDE*	rs10882101	10	94462427	T	C	0.587	1.06 (1.04–1.08)	[93,94]
341	*FAM49A*	rs11680058	2	16574669	A	G	0.863	1.06 (1.04–1.08)	[93,94]
342	*TSC22D2*	rs62271373	3	150066540	A	T	0.055	1.09 (1.06–1.12)	[93–95]
343	*TCF4*	rs72926932	18	53050646	C	A	0.08	1.09 (1.07–1.12)	[93–95]
344	*TFAP2B*	rs3798519	6	50788778	C	A	0.18	1.06 (1.04–1.08)	[93–95]
345	*SEC16B*	rs539515	1	177889025	C	A	0.198	1.05 (1.04–1.07)	[93–95]
346	*AOC1*	rs62492368	7	150537635	A	G	0.31	1.05 (1.03–1.06)	[93–95]
347	*ABCB10, ABCB10-NUP133*	rs348330	1	229672955	G	A	0.36	1.05 (1.04–1.07)	[93–95]
348	*SMEK1*	rs8010382	14	91963722	G	A	0.42	1.04 (1.03–1.05)	[93–95]
349	*CACNA2D3*	rs76263492	3	54828827	T	G	0.45	1.09 (1.06–1.13)	[93–95]
350	*USP3*	rs7178762	15	63871292	C	T	0.46	1.04 (1.03–1.05)	[93–95]
351	*LRFN2*	rs34298980	6	40409243	T	C	0.49	1.04 (1.03–1.05)	[93–95]
352	*ST6GAL1*	rs3887925	3	186665645	T	C	0.55	1.07 (1.05–1.08)	[93–95]
353	*PROX1*	rs340874	1	214159256	C	T	0.556	1.07 (1.05–1.08)	[93–95]
354	*MAP2K5*	rs4776970	15	68080886	A	T	0.64	1.04 (1.03–1.05)	[93–95]
355	*TTLL6, GIP–TTLL6*	rs35895680	17	47060322	C	A	0.678	1.06 (1.04–1.07)	[93–95]
356	*LYPLAL1*	rs2820446	1	219748818	C	G	0.71	1.06 (1.04–1.07)	[93–95]
357	*WSCD2*	rs1426371	12	108629780	G	A	0.74	1.05 (1.04–1.07)	[93–95]
358	*RNF6*	rs34584161	13	26776999	A	G	0.76	1.05 (1.03–1.06)	[93–95]
359	*SSR1–RREB1*	rs9379084	6	7231843	G	A	0.89	1.11 (1.08–1.13)	[93–95]
360	*CCND2*	rs76895963	12	4384844	T	G	0.98	1.62 (1.54–1.71)	[93–95]
361	*CDC123/CAMK1D, RN7SL232P*	rs11257655	10	12307894	T	C	0.218	1.09 (1.08–1.11)	[93–95]
362	*CENPW, CENPW–SOGA3*	rs11759026	6	126792095	G	A	0.232	1.07 (1.05–1.08)	[93–95]
363	*CDKN1B*	rs2066827	12	12871099	G	T	0.235	1.05 (1.03–1.06)	[93–95]
364	*MTNR1B*	rs10830963	11	92708710	G	C	0.277	1.10 (1.09–1.12)	[93–95]
365	*NEUROG3, VPS26A–NEUROG3*	rs177045	10	71321279	G	A	0.316	1.07 (1.05–1.08)	[93–95]
366	*LINGO2*	rs1412234	9	28410683	C	T	0.323	1.04 (1.03–1.06)	[93–95]
367	*UBAP2*	rs12001437	9	34074476	C	T	0.372	1.04 (1.03–1.06)	[93–95]
368	*PTGFRN*	rs1127215	1	117532790	C	T	0.584	1.05 (1.04–1.06)	[93–95]
369	*GCKR*	rs1260326	2	27730940	C	T	0.607	1.07 (1.06–1.08)	[93–95]
370	*BCL2A*	rs12454712	18	60845884	T	C	0.614	1.05 (1.04–1.06)	[93–95]
371	*PATJ, INADL*	rs12140153	1	62579891	G	T	0.905	1.07 (1.04–1.09)	[93–95]
372	*TLE1, RP11–154D17.1*	rs2796441	9	84308948	G	A	0.59	1.07 (1.05–1.08)	[93–95]
373	*QKI, RP1–230L10.1*	rs4709746	6	164133001	C	T	0.87	1.06 (1.04–1.08)	[93–95]
374	*CRHR2*	rs917195	7	30728452	C	T	0.77	1.05 (1.04–1.07)	[93–95]

(*continued*)

Table 12.2 (*Continued*)

slno	Nearest gene (*=BMI adjusted)	Index variant	Chromosome	Position (Build 37 bp)	Risk allele	Other allele	RAF (%)	OR (95% CI)/ beta (se)#	Reference
375	*TOMM40/APOE*	rs429358	19	45411941	T	C	0.846	1.08 (1.06–1.10)	[93,95]
376	*ANKH*	rs78408340/rs146886108	5	14751305	C	T	0.99	1.41 (1.28–1.55)	[93,95]
377	*HTT*	rs362307	4	3241845	T	C	0.077	1.08 (1.05–1.10)	[93,95]
378	*KCNQ1*	rs231361	11	2691500	A	G	0.26	1.08 (1.07–1.10)	[93,95]
379	*PVT1, RP11–89M16.1*	rs1561927	8	129568078	C	T	0.27	1.04 (1.03–1.06)	[93,95]
380	*CTTNBP2*	rs6976111	7	117495667	A	C	0.31	1.04 (1.03–1.06)	[93,95]
381	*LAMA1*	rs7240767	18	7070642	C	T	0.38	1.04 (1.02–1.05)	[93,95]
382	*INS/IGF2, TH*	rs4929965	11	2197286	A	G	0.38	1.07 (1.06–1.09)	[93,95]
383	*PIK3R1**	rs4976033	5	67714246	G	A	0.41	1.05 (1.03–1.06)	[93,95]
384	*ABCC5*	rs2872246	3	183738460	A	C	0.45	1.04 (1.02–1.05)	[93,95]
385	*MAEA*	rs56337234	4	1784403	C	T	0.5	1.06 (1.04–1.07)	[93,95]
386	*PLEKHA1*	rs2280141	10	124193181	T	G	0.52	1.05 (1.03–1.06)	[93,95]
387	*ROBO2*	rs2272163	3	77671721	C	A	0.618	1.04 (1.02–1.05)	[93,95]
388	*ZBTB46**	rs6011155	20	62450664	T	C	0.63	1.04 (1.02–1.05)	[93,95]
389	*PDGFC*	rs28819812	4	157652753	C	A	0.68	1.04 (1.03–1.06)	[93,95]
390	*HNF1A*	rs56348580	12	121432117	G	C	0.69	1.05 (1.04–1.07)	[93,95]
391	*FAM63A, BNIPL*	rs145904381	1	151017991	T	C	0.99	1.19 (1.12–1.26)	[93,95]
392	*CRYBA2**	rs113414093	2	219859171	A	G	0.051	1.12 (1.08–1.17)	[93,95]
393	*PIM3*	rs1801645	22	50356850	C	T	0.275	1.04 (1.02–1.05)	[93,95]
394	*ETS1*	rs10750397	11	128234144	A	G	0.282	1.05 (1.04–1.07)	[93,95]
395	*FTO*	rs1421085	16	53800954	C	T	0.415	1.13 (1.12–1.15)	[93,95]
396	*GNPDA2*	rs10938398	4	45186139	A	G	0.429	1.05 (1.03–1.06)	[93,95]
397	*WFS1*	rs10937721	4	6306763	C	G	0.588	1.06 (1.04–1.08)	[93,95]
398	*ANK1, NKX6–3*	rs13262861	8	41508577	C	A	0.829	1.07 (1.05–1.09)	[93,95]
399	*LPL*	rs10096633	8	19830921	C	T	0.877	1.07 (1.05–1.09)	[93,95]
400	*CASC11*	rs17772814	8	128711742	G	A	0.915	1.08 (1.05–1.11)	[93,95]
401	*TCF7L2*	rs7903146	10	114758349	C	T	0.71	1.37 (1.35–1.39)	[93,95]
402	*KCNQ1, INS–IGF2–KCNQ1*	rs2237897	11	2858546	C	T	0.95	1.23 (1.19–1.27)	[93–95]
403	*ADCY5*	rs11708067	3	123065778	A	G	0.772	1.09 (1.08–1.11)	[93–95]
404	*DMGDH*	rs10052346	5	78,472,599	G	T	–	1.04 (1.03–1.05)	[94]
405	*RBSM1*	rs1020731	2	161,144,055	A	G	–	1.03 (1.02–1.04)	[94]
406	*CYTH1*	rs1044486	17	76,792,179	G	A	–	1.04 (1.03–1.05)	[94]
407	*NF1*	rs1048317	17	29,704,002	T	C	–	1.04 (1.03–1.05)	[94]
408	*ARHGAP19–SLIT1*	rs10748694	10	99,056,190	A	T	–	1.04 (1.03–1.05)	[94]
409	*TRIM66*	rs10769936	11	8,654,528	C	T	–	1.03 (1.02–1.04)	[94]
410	*LDHB–KCNJ8*	rs10841890	12	21,871,751	–	–	–	–	[94]
411	*VWA5B1*	rs10916784	1	20,729,451	G	C	–	1.03 (1.02–1.05)	[94]
412	*ZNF281*	rs10919928	1	200,416,099	A	G	–	1.03 (1.02–1.05)	[94]
413	*MPPED2*	rs11031140	11	30,608,133	–	–	–	–	[94]
414	*RAI1*	rs1108646	17	17,751,478	A	G	–	1.04 (1.03–1.05)	[94]
415	*TRAF3*	rs11160699	14	103,252,270	A	G	–	1.04 (1.03–1.05)	[94]
416	*PTCH1*	rs113154802	9	98,278,413	C	T	–	1.05 (1.04–1.07)	[94]
417	*PGM1*	rs11576729	1	64,114,429	G	T	–	1.05 (1.04–1.06)	[94]
418	*CHD1L*	rs11588753	1	146,714,427	–	–	–	–	[94]
419	*GLI2*	rs11677557	2	121,317,747	–	–	–	–	[94]
420	*HNF1A*	rs1169299	12	121,429,194	–	–	–	–	[94]

421	*GP2*	rs117267808	16	20,323,168	–	–	–	–	[94]
422	*NKX6–1–CDS1*	rs117624659	4	85,339,618	T	C	–	1.24 (1.17–1.31)	[94]
423	*ATG16L1–DGKD*	rs117809958	2	234,191,103	A	T	–	1.24 (1.16–1.31)	[94]
424	*ETS1*	rs11819995	11	128,389,391	T	C	–	1.05 (1.04–1.06)	[94]
425	*RASA1*	rs11953892	5	86,518,243	–	–	–	–	[94]
426	*BRAF*	rs11983228	7	140,631,823	C	G	–	1.05 (1.04–1.07)	[94]
427	*FAF1*	rs12073283	1	51,219,188	C	G	–	1.08 (1.06–1.09)	[94]
428	*ST7L*	rs12137269	1	113,106,633	–	–	–	–	[94]
429	*SPRY2*	rs1215468	13	80,707,429	A	G	–	1.08 (1.07–1.10)	[94]
430	*ZNF169*	rs12345069	9	96,971,175	C	T	–	1.04 (1.03–1.05)	[94]
431	*CELF1*	rs12361415	11	47,474,146	–	–	–	–	[94]
432	*SCHLAP1*	rs12479357	2	181,570,507	–	–	–	–	[94]
433	*KLHDC5*	rs12578595	12	27,964,996	C	T	–	1.07 (1.06–1.08)	[94]
434	*KCNH7*	rs12614955	2	163,649,480	T	C	–	1.03 (1.02–1.04)	[94]
435	*PXK*	rs12629058	3	58,338,809	T	C	–	1.04 (1.02–1.05)	[94]
436	*GCC1–PAX4–LEP*	rs12669223	7	127,250,831	A	G	–	1.21 (1.17–1.25)	[94]
437	*LONRF1*	rs12680692	8	12,618,225	A	T	–	1.03 (1.02–1.04)	[94]
438	*SIX3–SIX2*	rs12712928	2	45,192,080	C	G	–	1.01 (1.00–1.02)	[94]
439	*RASGRP1*	rs12912777	15	38,852,386	–	–	–	–	[94]
440	*GRB10*	rs13236710	7	50,809,085	G	A	–	1.05 (1.03–1.07)	[94]
441	*TLE4*	rs13290396	9	81,914,978	C	T	–	1.10 (1.08–1.12)	[94]
442	*THADA*	rs13414140	2	43,671,176	C	T	–	1.09 (1.07–1.11)	[94]
443	*LOC541471*	rs1345203	2	112,253,851	–	–	–	–	[94]
444	*ZNF257*	rs142395395	19	22,100,706	A	G	–	1.23 (1.17–1.30)	[94]
445	*PDGFC*	rs1425482	4	157,725,916	T	C	–	1.03 (1.02–1.04)	[94]
446	*ZBTB20*	rs1459513	3	114,960,798	C	A	–	1.05 (1.04–1.07)	[94]
447	*LTK*	rs1473781	15	41,818,917	A	G	–	1.03 (1.02–1.04)	[94]
448	*DMRT2*	rs1509195	9	1,033,958	–	–	–	–	[94]
449	*BEND3*	rs1665901	6	107,433,400	A	T	–	1.04 (1.03–1.05)	[94]
450	*IKZF2*	rs16849467	2	213,818,731	T	C	–	1.04 (1.02–1.05)	[94]
451	*BNIPL*	rs17049712	2	58,961,136	T	C	–	1.03 (1.02–1.05)	[94]
452	*FOXN3*	rs17714667	14	89,550,378	–	–	–	–	[94]
453	*MPHOSPH9–ZNF664*	rs1790116	12	123,618,544	T	G	–	1.04 (1.03–1.06)	[94]
454	*CDH7*	rs1942267	18	63,416,719	–	–	–	–	[94]
455	*TSEN15*	rs1952256	1	184,035,116	–	–	–	–	[94]
456	*ACSL1*	rs1996546	4	185,714,289	G	T	–	1.06 (1.05–1.08)	[94]
457	*FOXA2*	rs2181063	20	22,427,370	C	G	–	1.03 (1.02–1.05)	[94]
458	*SLC9B1*	rs223423	4	103,725,894	G	A	–	1.02 (1.01–1.03)	[94]
459	*LOC646588–NFE2L3*	rs2391174	7	25,979,338	–	–	–	–	[94]
460	*STRBP*	rs2416899	9	126,015,103	T	G	–	1.03 (1.02–1.05)	[94]
461	*PLEKHA1*	rs2421016	10	124,167,512	C	T	–	1.04 (1.03–1.05)	[94]
462	*FGFR4–NSD1*	rs244708	5	176,589,585	G	A	–	1.03 (1.02–1.04)	[94]
463	*AUTS2*	rs2533457	7	69,055,951	G	A	–	1.04 (1.03–1.05)	[94]
464	*RBM6*	rs2624847	3	50,174,197	G	T	–	1.03 (1.02–1.05)	[94]
465	*UHRF1–PTPRS*	rs262549	19	4,951,064	G	C	–	1.05 (1.03–1.06)	[94]
466	*PPP3CA*	rs2659518	4	102,135,363	A	G	–	1.04 (1.03–1.05)	[94]
467	*FOXK1*	rs28411900	7	4,691,060	–	–	–	–	[94]
468	*PIM3*	rs28691713	22	50,356,302	C	T	–	1.05 (1.04–1.06)	[94]

(*continued*)

Table 12.2 (*Continued*)

slno	Nearest gene (*=BMI adjusted)	Index variant	Chromosome	Position (Build 37 bp)	Risk allele	Other allele	RAF (%)	OR (95% CI)/ beta (se)#	Reference
469	*PRC1*	rs2890156	15	91,513,157	A	T	–	1.07 (1.06–1.08)	[94]
470	*IRS1*	rs2943648	2	227,100,490	G	A	–	1.09 (1.07–1.10)	[94]
471	*MAST2*	rs34444543	1	46,358,862	G	A	–	1.04 (1.02–1.05)	[94]
472	*MTMR3–ZNRF3*	rs36575	22	30,205,572	C	T	–	1.08 (1.06–1.11)	[94]
473	*INFAM2*	rs3743140	15	40,616,742	A	G	–	1.05 (1.03–1.06)	[94]
474	*MACF1*	rs3768301	1	39,870,793	T	C	–	1.07 (1.06–1.08)	[94]
475	*GDAP1*	rs3780012	8	75,147,209	C	G	–	1.14 (1.09–1.19)	[94]
476	*SH2B3–ALDH2–BRAP*	rs3782886	12	112,110,489	T	C	–	1.06 (1.04–1.09)	[94]
477	*MYO5C*	rs3825801	15	52,517,714	C	T	–	1.05 (1.03–1.06)	[94]
478	*BOP1*	rs3890400	8	145,544,720	A	G	–	1.04 (1.03–1.06)	[94]
479	*MSRA–XKR6*	rs4240673	8	10,787,612	T	C	–	1.04 (1.03–1.05)	[94]
480	*CEP120*	rs4267865	5	122,704,342	G	T	–	1.08 (1.05–1.10)	[94]
481	*PPIP5K1*	rs475486	15	43,850,486	–	–	–	–	[94]
482	*CCDC39–FXR1*	rs4854992	3	180,545,384	–	–	–	–	[94]
483	*RALY*	rs4911405	20	32,674,967	T	C	–	1.04 (1.03–1.05)	[94]
484	*BDNF*	rs4923464	11	27,683,618	C	T	–	1.03 (1.02–1.04)	[94]
485	*ANK1*	rs508419	8	41,522,991	G	A	–	1.05 (1.04–1.07)	[94]
486	*DTNB*	rs55928417	2	25,533,568	G	T	–	1.03 (1.02–1.05)	[94]
487	*PIK3R1*	rs57634870	5	67,716,793	G	T	–	1.04 (1.03–1.06)	[94]
488	*PSMA3*	rs61450169	14	58,712,860	–	–	–	–	[94]
489	*C11orf30*	rs61894507	11	76,156,973	G	A	–	1.04 (1.02–1.05)	[94]
490	*ZFHX3*	rs6416749	16	73,100,308	C	T	–	1.04 (1.03–1.05)	[94]
491	*FOLH1*	rs6485981	11	49,477,266	T	C	–	1.04 (1.03–1.06)	[94]
492	*PKP2–SYT10*	rs6488140	12	33,370,406	A	G	–	1.04 (1.02–1.05)	[94]
493	*HIVEP2*	rs6570526	6	143,058,692	G	C	–	1.03 (1.02–1.04)	[94]
494	*PENK*	rs6651357	8	57,498,704	–	–	–	–	[94]
495	*DSTYK–MDM4*	rs6689629	1	204,539,291	A	G	–	1.04 (1.02–1.05)	[94]
496	*CEP68*	rs6752053	2	65,666,674	T	C	–	1.05 (1.04–1.06)	[94]
497	*MLX*	rs684214	17	40,696,915	T	C	–	1.04 (1.03–1.05)	[94]
498	*LCORL*	rs6855926	4	18,047,401	A	G	–	1.04 (1.03–1.05)	[94]
499	*RGS17*	rs6932473	6	153,438,573	T	A	–	1.04 (1.03–1.05)	[94]
500	*PSMD6–ADAMTS9*	rs704360	3	63,884,800	–	–	–	–	[94]
501	*BBIP1*	rs7067540	10	112,621,837	–	–	–	–	[94]
502	*RGMA*	rs7167984	15	93,832,067	–	–	–	–	[94]
503	*CFAP61*	rs7261425	20	20,068,635	–	–	–	–	[94]
504	*LRRC74A*	rs72627178	14	77,372,210	–	–	–	–	[94]
505	*BCAR1*	rs72802358	16	75,243,657	–	–	–	–	[94]
506	*TSPAN8*	rs7313668	12	71,449,521	–	–	–	–	[94]
507	*DLK1–MEG3*	rs73347525	14	101,255,172	–	–	–	–	[94]
508	*EP300*	rs738630	22	41,511,171	–	–	–	–	[94]
509	*TFRC*	rs74289356	3	195,825,077	–	–	–	–	[94]
510	*EBF1*	rs748510	5	158,025,983	–	–	–	–	[94]
511	*PDE3A*	rs7488780	12	20,579,392	–	–	–	–	[94]
512	*CYTIP*	rs7594480	2	158,390,468	–	–	–	–	[94]
513	*ARL15*	rs7736354	5	53,297,591	–	–	–	–	[94]
514	*MED23-ENPP3*	rs7739842	6	131,954,797	–	–	–	–	[94]

515	*JARID2*	rs7769291	6	15,499,419	–	–	–	–	[94]
516	*PTPN11-HECTD4*	rs77753011	12	113,117,897	–	–	–	–	[94]
517	*LPL*	rs7819706	8	19,844,415	–	–	–	–	[94]
518	*MYO3A*	rs7923442	10	26,497,704	–	–	–	–	[94]
519	*RMST*	rs7972074	12	97,851,611	–	–	–	–	[94]
520	*TRPS1*	rs800909	8	116,497,173	–	–	–	–	[94]
521	*TCF12*	rs8024992	15	57,590,203	–	–	–	–	[94]
522	*NOTCH2*	rs835576	1	120,455,586	–	–	–	–	[94]
523	MHC region	rs879882	6	31,139,452	–	–	–	–	[94]
524	*REPS1*	rs9376353	6	138,855,975	–	–	–	–	[94]
525	*ZNF713*	rs9784904	7	55,835,078	–	–	–	–	[94]
526	*LEKR1-CCNL1*	rs9854955	3	156,795,525	–	–	–	–	[94]
527	*LAMA1*	rs9948462	18	7,076,836	–	–	–	–	[94]
528	*WFS1*	rs9998835	4	6,293,237	–	–	–	–	[94]
529	*ZNF503-LRMDA*	rs3012060	10	77,244,336	T	A	0.185	0.0342(0.0055)	[94, 95]
530	*CTBP1-PCGF3-MAEA*	rs730831	4	1,240,299	G	T	0.195	–0.0878(0.0072)	[94, 95]
531	*TET2*	rs17035289	4	106,048,291	C	T	0.206	0.0357(0.0048)	[94, 95]
532	*SGCG*	rs314879	13	23,309,382	C	T	0.229	0.0364(0.0046)	[94, 95]
533	*GRP-MC4R, RNU4-17P*	rs6567160	18	57,829,135	C	T	0.236	0.0539(0.0044)	[94, 95]
534	*KCNU1, RP11-150O12.1*	rs12680217	8	37,397,803	C	T	0.301	–0.0397(0.0071)	[94, 95]
535	*BCL11A, AC007381.2*	rs243018	2	60,586,707	G	C	0.504	0.0508(0.0039)	[94, 95]
536	*CRY2*	rs12419690	11	45,858,584	G	A	0.512	0.0298(0.004)	[94, 95]
537	*ZFAND3-KCNK16-GLP1R, KCNK17*	rs34247110	6	39,282,371	G	A	0.516	–0.0305(0.0038)	[94, 95]
538	*AKAP6*	rs12883788	14	33,303,540	C	T	0.589	–0.0327(0.004)	[94, 95]
539	*GRB14, COBLL1*	rs10184004	2	165,508,389	C	T	0.595	0.0636(0.0041)	[94, 95]
540	*FAIM2*	rs7132908	12	50,263,148	G	A	0.643	–0.0297(0.004)	[94, 95]
541	*TMEM154*	rs6813195	4	153,520,475	C	T	0.649	0.0463(0.004)	[94, 95]
542	*ZFPM1*	rs9937296	16	88,554,480	C	T	0.771	0.0445(0.007)	[94, 95]
543	*MAP3K11, LTBP3*	rs12789028	11	65,326,154	G	A	0.820	–0.0459(0.005)	[94, 95]
544	*TPCN2-CCND1*	rs3918298	11	69,463,273	G	A	0.882	0.1038(0.0101)	[94, 95]
545	*CILP2-TM6SF2*	rs58542926	19	19,379,549	C	T	0.926	–0.0721(0.0072)	[94, 95]
546	NA	NA	2	149428856	T	A	0.426	–0.0501(0.009)	[95]
547	NA	NA	22	40541838	C	T	0.467	–0.0225(0.004)	[95]
548	NA	NA	16	20334808	C	A	0.910	–0.1004(0.0156)	[95]
549	NA	NA	8	97724430	G	T	0.992	–0.2392(0.0348)	[95]
550	COPB1	rs117316450	11	14518419	G	C	0.018	0.1328(0.0171)	[95]
551	DNAJC2	rs187653072	7	102976385	C	T	0.027	0.0967(0.0138)	[95]
552	—	rs114136102	5	36084426	C	T	0.038	0.0631(0.0114)	[95]
553	ZBTB38	rs56243018	3	141101839	C	A	0.046	–0.0833(0.0104)	[95]
554	RP11-115J16.2	rs17662402	8	9265105	C	T	0.053	–0.067(0.01)	[95]
555	OR5D18	rs116861182	11	55588216	C	A	0.053	0.0615(0.0105)	[95]
556	—	rs144052331	5	122650885	C	T	0.054	–0.0709(0.0098)	[95]
557	—	rs1528287	12	80985872	G	T	0.059	–0.494(0.08)	[95]
558	OR4C9P	rs149027146	11	48489360	T	A	0.060	0.0738(0.0104)	[95]
559	BRAF	rs60251368	7	140522073	G	A	0.068	0.0549(0.0078)	[95]
560	RP11-127H5.1	rs112515915	8	105662373	G	A	0.069	–0.0562(0.0085)	[95]
561	STAU2	rs28792187	8	74568099	G	A	0.073	0.0414(0.0076)	[95]
562	THADA	rs76675804	2	43611883	C	T	0.094	–0.1208(0.0074)	[95]

(*continued*)

Table 12.2 (*Continued*)

slno	Nearest gene (*=BMI adjusted)	Index variant	Chromosome	Position (Build 37 bp)	Risk allele	Other allele	RAF (%)	OR (95% CI)/ beta (se)#	Reference
563	—	rs2780215	6	34236973	G	A	0.100	–0.0531(0.0091)	[95]
564	BCL2L11	rs113135335	2	111887754	G	T	0.104	–0.0533(0.0073)	[95]
565	—	rs71495046	10	33997227	C	A	0.121	0.0399(0.0063)	[95]
566	—	rs11561066	11	50110597	C	T	0.130	0.0451(0.0065)	[95]
567	RFX3	rs75619936	9	3249708	G	C	0.133	0.0314(0.0056)	[95]
568	—	rs9308614	2	121337196	G	A	0.134	–0.057(0.0058)	[95]
569	PRIM1	rs2277339	12	57146069	G	T	0.143	0.0437(0.0056)	[95]
570	RANBP17	rs2913873	5	170683134	G	A	0.144	–0.0316(0.0056)	[95]
571	EBF2	rs11998023	8	25871721	G	T	0.177	0.0324(0.0053)	[95]
572	PTEN	rs36062478	10	89722731	C	T	0.178	0.0389(0.0054)	[95]
573	FAM60A	rs80234489	12	31441179	C	A	0.180	0.0966(0.0112)	[95]
574	NUS1	rs80196932	6	117996631	C	T	0.183	–0.0479(0.0053)	[95]
575	TRPV5	rs4252505	7	142607301	G	A	0.185	0.0413(0.007)	[95]
576	SORBS2	rs35901985	4	186580062	G	A	0.185	–0.0332(0.0053)	[95]
577	ZHX3	rs17265513	20	39832628	C	T	0.189	0.0327(0.0055)	[95]
578	*AR;OPHN1*	–	X	67255974	C	T	0.189	0.104(0.019)	[95]
579	SEC23IP	rs11199116	10	121660400	C	A	0.191	0.0306(0.005)	[95]
580	—	rs7538321	1	205789455	T	A	0.195	0.0287(0.0051)	[95]
581	TRIM63	rs9438610	1	26396065	G	A	0.197	–0.0313(0.0051)	[95]
582	—	rs2583938	12	66215214	T	A	0.197	–0.123(0.018)	[95]
583	LINC00910	rs56799554	17	41456413	G	A	0.197	0.0327(0.0049)	[95]
584	—	rs7071036	10	122930568	C	T	0.198	–0.051(0.0073)	[95]
585	—	rs2216063	16	54387084	G	A	0.198	–0.0296(0.0054)	[95]
586	NEGR1	rs2613499	1	72751552	G	A	0.199	–0.0363(0.0053)	[95]
587	ATXN7	rs13434089	3	63948566	C	T	0.203	–0.0607(0.0052)	[95]
588	NFIB	rs73642097	9	14141703	G	A	0.205	0.0291(0.0049)	[95]
589	C9orf3	rs6479591	9	97795421	G	A	0.205	–0.0326(0.0054)	[95]
590	—	rs9319943	18	56879827	C	T	0.207	–0.0308(0.0048)	[95]
591	GGNBP1	rs75080135	6	33552707	C	A	0.207	–0.0357(0.0049)	[95]
592	PLEKHM2	rs12746673	1	16050470	C	A	0.208	0.0308(0.0049)	[95]
593	LHFPL3	rs73184014	7	104516274	G	A	0.209	–0.0298(0.0052)	[95]
594	—	rs2188848	7	23884697	G	A	0.211	–0.0325(0.0048)	[95]
595	LINC00907	rs410150	18	40066006	C	T	0.214	0.0289(0.0048)	[95]
596	*SPIN2A;FAAH2*	–	X	56759371	T	G	0.218	0.069(0.013)	[95]
597	MICF	rs2394186	6	29816421	G	A	0.219	–0.0271(0.0048)	[95]
598	RN7SKP15	rs3751239	12	27963676	G	C	0.219	–0.0687(0.0047)	[95]
599	EPB41L4B	rs10119430	9	111938268	G	A	0.221	0.0279(0.0046)	[95]
600	*IL13RA1*	–	X	117877437	A	G	0.223	0.118(0.013)	[95]
601	STRC	rs2447198	15	43895118	C	T	0.224	–0.034(0.0055)	[95]
602	RBMS1	rs6710938	2	161333872	C	A	0.228	–0.0342(0.0046)	[95]
603	*IL13RA1*	–	X	117955250	T	C	0.231	0.077(0.01)	[95]
604	STAG1	rs667920	3	136069472	G	T	0.233	–0.0324(0.0045)	[95]
605	JARID2	rs727734	6	15475051	T	A	0.236	–0.0292(0.0045)	[95]
606	REV3L	rs55812705	6	111738793	C	T	0.238	–0.0301(0.005)	[95]
607	RNU6-1231P	rs2482506	10	104563743	G	C	0.239	–0.0316(0.0045)	[95]
608	—	rs11236524	11	75464344	C	T	0.241	0.0363(0.0064)	[95]
609	—	rs9560114	13	112187882	T	A	0.244	–0.0259(0.0047)	[95]
610	IPO9	rs41304257	1	201849926	G	A	0.244	–0.0318(0.0047)	[95]

611	AC016903.2	rs4482463	2	205375909	C	A	0.244	0.0316(0.0056)	[95]
612	*CCNQ;DUSP9*	–	X	152898928	C	A	0.247	−0.163(0.012)	[95]
613	LINC01141	rs10916780	1	20707153	G	A	0.248	−0.0342(0.0046)	[95]
614	CBX1	rs3744347	17	46178674	G	A	0.253	−0.0301(0.0046)	[95]
615	DTNB	rs34845373	2	25635771	G	A	0.256	−0.0334(0.0048)	[95]
616	LMF1	rs12918782	16	967241	G	A	0.257	0.0308(0.0047)	[95]
617	HAT1	rs62182438	2	172796774	T	A	0.260	0.0257(0.0045)	[95]
618	—	rs13365225	8	36858483	G	A	0.261	0.0327(0.0046)	[95]
619	—	rs9515905	13	91949562	G	A	0.261	−0.0472(0.0044)	[95]
620	RFT1	rs62255926	3	53125429	T	A	0.263	−0.0252(0.0046)	[95]
621	—	rs12539264	7	48839003	G	A	0.266	0.029(0.0045)	[95]
622	CMIP	rs56823429	16	81533789	C	A	0.269	0.0418(0.0045)	[95]
623	ERBB4	rs3828242	2	212274937	G	A	0.270	−0.0252(0.0043)	[95]
624	—	rs10469860	2	105165674	G	A	0.276	−0.0238(0.0043)	[95]
625	*AR;EDA2R*	–	X	66168667	A	G	0.277	0.082(0.011)	[95]
626	RP11-346C20.3	rs1075855	16	73098091	G	C	0.279	0.0263(0.0045)	[95]
627	—	rs62490267	7	149238823	C	T	0.279	0.031(0.0057)	[95]
628	*GPC3;GPC4*	–	X	132597984	C	T	0.282	0.135(0.024)	[95]
629	—	rs7781440	7	50887174	C	T	0.284	−0.086(0.015)	[95]
630	AC079610.1	rs4673712	2	213829721	C	T	0.290	−0.0269(0.0045)	[95]
631	*EDA2R*	–	X	66316809	G	A	0.29	0.077(0.013)	[95]
632	RP5-899E9.1	rs12669521	7	77047102	G	A	0.296	−0.0263(0.0044)	[95]
633	—	rs34617913	4	44503503	G	A	0.297	−0.0239(0.0043)	[95]
634	DDC	rs73121277	7	50577968	C	T	0.297	0.026(0.0042)	[95]
635	GLP2R	rs17810376	17	9787845	G	A	0.297	0.0279(0.0047)	[95]
636	—	rs6741676	2	181618654	G	A	0.307	−0.0324(0.0042)	[95]
637	BPTF	rs12603589	17	65825248	C	T	0.313	0.0421(0.0046)	[95]
638	MAML3	rs12505942	4	140906390	C	T	0.313	−0.0294(0.0042)	[95]
639	RPTOR	rs11150745	17	78757626	G	A	0.317	−0.0312(0.0053)	[95]
640	—	rs6712905	2	196952010	C	T	0.318	0.0279(0.0042)	[95]
641	CTB-12O2.1	rs302395	5	151324600	G	T	0.322	0.0232(0.0041)	[95]
642	BBIP1	rs7895872	10	112678657	G	T	0.323	−0.0306(0.0041)	[95]
643	*BCLAF3;MAP7D2*	–	X	20009166	T	C	0.323	0.058(0.01)	[95]
644	OR5B17	rs7483027	11	58128015	C	T	0.328	−0.0267(0.0041)	[95]
645	PHF13	rs11583755	1	6672729	C	A	0.329	0.0369(0.0041)	[95]
646	MAML2	rs7130522	11	95710493	C	A	0.329	0.0222(0.0041)	[95]
647	GUCY1B3	rs2125799	4	156697784	C	T	0.331	0.0244(0.0041)	[95]
648	—	rs6549112	3	86756871	G	T	0.333	−0.0268(0.004)	[95]
649	CCDC92	rs4930726	12	124428331	C	T	0.334	−0.0353(0.0041)	[95]
650	—	rs9390022	6	143056556	C	T	0.336	−0.0306(0.0041)	[95]
651	—	rs7147483	14	38804675	C	T	0.336	−0.0352(0.0041)	[95]
652	SGCZ	rs35753840	8	14148990	C	A	0.340	0.0254(0.0042)	[95]
653	AC142119.1	rs28758542	2	16238001	G	A	0.341	−0.0256(0.0042)	[95]
654	*DMD*	–	X	31851610	T	C	0.343	0.047(0.009)	[95]
655	—	rs11159347	14	25947436	C	T	0.344	−0.0248(0.0041)	[95]
656	CICP11	rs6972291	7	55802063	C	T	0.346	0.0283(0.0048)	[95]
657	MNAT1	rs4902002	14	61229411	G	A	0.347	0.0246(0.0041)	[95]
658	FEN1	rs174541	11	61565908	C	T	0.349	−0.0277(0.0041)	[95]
659	—	rs4463416	8	34502571	C	A	0.352	−0.0237(0.0041)	[95]

(*continued*)

Table 12.2 (*Continued*)

slno	Nearest gene (*=BMI adjusted)	Index variant	Chromosome	Position (Build 37 bp)	Risk allele	Other allele	RAF (%)	OR (95% CI)/ beta (se)#	Reference
660	MED27	rs9411425	9	134868417	G	T	0.353	0.0236(0.004)	[95]
661	EVA1B	rs12116935	1	36789546	G	A	0.354	0.0242(0.0043)	[95]
662	BDNF	rs10767659	11	27686196	G	T	0.354	0.026(0.0042)	[95]
663	SHROOM3	rs56281442	4	77533939	G	A	0.356	−0.025(0.0044)	[95]
664	—	rs7645613	3	115063672	C	T	0.357	0.034(0.0048)	[95]
665	—	rs2908274	7	44185088	G	A	0.359	−0.089(0.014)	[95]
666	—	rs2943650	2	227105921	C	T	0.362	−0.0805(0.0042)	[95]
667	*RGAG1;CHRDL1*	–	X	109888390	A	C	0.364	−0.048(0.008)	[95]
668	SPHKAP	rs13415288	2	228971884	C	T	0.365	0.0262(0.004)	[95]
669	ABCC8	rs757110	11	17418477	C	A	0.370	0.0599(0.0039)	[95]
670	PKLR	rs3020781	1	155269776	G	A	0.372	0.0294(0.0043)	[95]
671	CRYBA1	rs9913225	17	27570622	G	A	0.374	0.0262(0.004)	[95]
672	—	rs11096542	2	18707873	G	A	0.376	−0.0254(0.0043)	[95]
673	ZNRF3	rs5762925	22	29369398	C	A	0.378	0.0267(0.0039)	[95]
674	RP1-85F18.5	rs11913442	22	41593581	C	T	0.380	−0.0245(0.004)	[95]
675	GTF2I	rs13238568	7	74076493	G	A	0.381	0.0248(0.0041)	[95]
676	CEP68	rs2723065	2	65279414	G	A	0.382	−0.0422(0.0039)	[95]
677	DGKD	rs838720	2	234303281	G	C	0.384	0.034(0.0039)	[95]
678	RP11-283G6.4	rs11048457	12	26463174	G	A	0.386	0.0385(0.0043)	[95]
679	—	rs6766859	3	138055136	C	T	0.386	0.0275(0.004)	[95]
680	TSPAN8	rs10879261	12	71520761	G	T	0.388	0.0341(0.0038)	[95]
681	ASTN2	rs1885234	9	119252277	G	T	0.395	0.0244(0.0039)	[95]
682	—	rs12586772	14	74932641	T	A	0.396	−0.0228(0.0039)	[95]
683	—	rs2816177	1	179248952	G	A	0.399	0.0224(0.0039)	[95]
684	—	rs6561273	13	46514492	G	C	0.400	−0.0303(0.0052)	[95]
685	RP11-44N17.2	rs510062	8	97138738	G	A	0.404	−0.022(0.0039)	[95]
686	PLXND1	rs2255703	3	129293256	C	T	0.404	−0.0256(0.0039)	[95]
687	C11orf30	rs2513505	11	76230357	C	A	0.407	−0.024(0.0038)	[95]
688	*ARHGEF6*	–	X	135859359	C	G	0.407	−0.049(0.008)	[95]
689	—	rs4384608	16	87856424	C	T	0.408	0.0266(0.0043)	[95]
690	—	rs242105	14	69459229	C	A	0.409	0.039(0.0059)	[95]
691	BEND7	rs11258422	10	13540869	C	A	0.409	0.0241(0.0041)	[95]
692	—	rs10844519	12	33410855	G	T	0.409	0.03(0.0042)	[95]
693	AOAH	rs6978327	7	36742886	C	T	0.411	−0.0233(0.004)	[95]
694	GINS2	rs11646052	16	85716463	G	A	0.412	0.026(0.0039)	[95]
695	—	rs978444	3	93981060	G	T	0.414	0.0229(0.0039)	[95]
696	CTD-2337A12.1	rs261967	5	95850250	C	A	0.414	0.0235(0.0038)	[95]
697	LAMC1	rs4129858	1	183004334	G	A	0.417	0.0223(0.0038)	[95]
698	RP11-452K12.4	rs945187	10	99091369	G	A	0.420	0.031(0.0039)	[95]
699	UBE2O	rs372558	17	74418176	G	C	0.420	−0.0213(0.0039)	[95]
700	ART3	rs4440243	4	77017680	C	T	0.422	−0.0246(0.0043)	[95]
701	TSHZ2	rs2252115	20	51620857	G	A	0.428	−0.0237(0.0039)	[95]
702	SUPT3H	rs538801	6	44875762	T	A	0.430	−0.0211(0.0039)	[95]
703	NUP160	rs3816605	11	47857253	C	T	0.436	−0.0318(0.0043)	[95]
704	ADAMTSL3	rs1812707	15	84547222	C	T	0.437	−0.0227(0.0039)	[95]
705	RP11-266O8.1	rs4777857	15	93925327	G	A	0.439	0.0255(0.0039)	[95]
706	ZMIZ1	rs697239	10	80947438	C	T	0.445	−0.0587(0.0038)	[95]

707	FAM227B	rs7169799	15	49794020	C	T	0.448	0.0213(0.0038)	[95]
708	RP1-167F1.2	rs10806906	6	19751516	C	T	0.448	0.0223(0.0039)	[95]
709	—	rs10787518	10	115821878	T	A	0.450	0.0292(0.0051)	[95]
710	NOL4	rs17747955	18	31582890	C	T	0.450	0.0224(0.004)	[95]
711	PNKD	rs1877712	2	219168432	G	A	0.452	0.0211(0.0039)	[95]
712	SRGAP2	rs61817176	1	206621028	C	A	0.453	−0.0263(0.004)	[95]
713	CALCR	rs10262104	7	93118736	C	T	0.458	0.022(0.0039)	[95]
714	IL34	rs13330163	16	70660243	G	A	0.458	−0.021(0.0038)	[95]
715	NF1	rs2040792	17	29628549	C	A	0.461	0.031(0.0039)	[95]
716	MYO19	rs1109442	17	34862220	C	T	0.463	0.0218(0.0037)	[95]
717	ANKRD28	rs924753	3	15706124	G	A	0.465	0.0263(0.0039)	[95]
718	AC004969.1	rs6956980	7	89803634	C	T	0.467	0.0284(0.0038)	[95]
719	HNF1B	rs11651755	17	36099840	C	T	0.467	0.0663(0.0038)	[95]
720	ATP8B2	rs1194592	1	154324384	G	C	0.469	−0.0242(0.0039)	[95]
721	CNTN2	rs11240351	1	205044339	G	A	0.470	0.0256(0.004)	[95]
722	—	rs12128213	1	200197538	G	A	0.471	−0.0256(0.0042)	[95]
723	LINC01122	rs12986742	2	58975143	C	T	0.473	0.0353(0.0038)	[95]
724	RMST	rs6538805	12	97849120	C	T	0.474	−0.0303(0.0039)	[95]
725	GRID1	rs11201992	10	88117318	C	A	0.477	0.0251(0.0038)	[95]
726	NHSL1	rs7742292	6	138864489	C	T	0.478	0.0261(0.004)	[95]
727	ACE	rs4335	17	61565025	G	A	0.478	0.0304(0.0038)	[95]
728	SGIP1	rs4655617	1	67010654	C	A	0.479	0.0256(0.004)	[95]
729	FAM13A	rs9991328	4	89713121	C	T	0.480	−0.0227(0.0038)	[95]
730	RBM6	rs6792892	3	49995518	C	T	0.482	0.0306(0.004)	[95]
731	CRTC1	rs10404726	19	18834514	C	T	0.483	0.0255(0.0042)	[95]
732	—	rs6716394	2	146350724	G	A	0.484	0.0275(0.0037)	[95]
733	RP11-349A22.5	rs12892257	14	58732748	G	A	0.486	0.0288(0.005)	[95]
734	HHIP	rs200995462	4	145612552	T	A	0.489	−0.0299(0.0047)	[95]
735	—	rs3845843	2	152198598	C	T	0.492	−0.0264(0.0038)	[95]
736	WNT8A	rs217256	5	137431501	C	T	0.493	0.021(0.0037)	[95]
737	—	rs9257408	6	28926220	G	C	0.493	−0.0314(0.0049)	[95]
738	ENO3	rs366577	17	4854480	C	T	0.494	0.0222(0.004)	[95]
739	CAMK2G	rs2633311	10	75598099	C	T	0.497	0.0237(0.004)	[95]
740	ZNF10	rs7970687	12	133730500	C	T	0.498	−0.026(0.0039)	[95]
741	RP11-624M8.1	rs7758115	6	126061502	G	A	0.500	−0.0232(0.0039)	[95]
742	SAT2	rs858519	17	7531965	C	T	0.505	−0.024(0.004)	[95]
743	PDZRN4	rs2730827	12	41863393	C	T	0.515	−0.0279(0.0038)	[95]
744	RPL35AP3	rs2876354	6	137295352	C	T	0.517	0.0465(0.0038)	[95]
745	—	rs9449295	6	64163807	C	T	0.517	0.0216(0.0039)	[95]
746	TET1	rs10998338	10	70382179	G	A	0.519	−0.0308(0.0039)	[95]
747	FIBCD1	rs6597649	9	133786652	C	T	0.520	−0.0234(0.0039)	[95]
748	CYTH1	rs7224711	17	76772288	C	T	0.520	0.0307(0.0038)	[95]
749	TMEM106B	rs13237518	7	12269593	C	A	0.521	−0.0283(0.0038)	[95]
750	RGS17	rs7758002	6	153440770	G	T	0.524	−0.0317(0.0039)	[95]
751	PML	rs9479	15	74328576	G	A	0.524	0.0271(0.0037)	[95]
752	ANKDD1B	rs34341	5	74934009	T	A	0.525	0.0403(0.0039)	[95]
753	—	rs2409742	8	11069960	C	T	0.526	0.0341(0.0042)	[95]
754	TRIM59	rs7629	3	160153305	G	A	0.528	−0.0311(0.0042)	[95]
755	FOCAD	rs2150999	9	20790622	C	T	0.537	0.0243(0.0039)	[95]
756	—	rs2408252	12	45868623	C	T	0.538	−0.0264(0.0043)	[95]

(*continued*)

Table 12.2 (*Continued*)

slno	Nearest gene (*=BMI adjusted)	Index variant	Chromosome	Position (Build 37 bp)	Risk allele	Other allele	RAF (%)	OR (95% CI)/ beta (se)#	Reference
757	PLEKHM3	rs34329895	2	208870017	G	A	0.538	–0.0255(0.004)	[95]
758	MFHAS1	rs4382480	8	8721473	G	A	0.539	–0.0306(0.0042)	[95]
759	—	rs9564268	13	66204880	C	T	0.544	–0.0243(0.004)	[95]
760	—	rs9587811	13	109946882	C	A	0.546	0.0248(0.0038)	[95]
761	TM4SF4	rs28712435	3	149221563	C	T	0.548	0.0254(0.0039)	[95]
762	YTHDF2	rs3753693	1	29060898	C	T	0.549	0.0255(0.004)	[95]
763	TPCN2	rs10750840	11	68835182	T	A	0.552	–0.0239(0.0039)	[95]
764	—	rs7912336	10	118558736	T	A	0.553	0.0217(0.0038)	[95]
765	RAI1	rs2297508	17	17715317	G	C	0.558	–0.0305(0.004)	[95]
766	—	rs3996350	7	130427057	G	C	0.559	0.0347(0.0039)	[95]
767	ERLIN1	rs1408579	10	101912194	C	T	0.559	0.0275(0.0042)	[95]
768	—	rs7787720	7	13886654	C	T	0.559	–0.0285(0.0039)	[95]
769	LINC00693	rs9869477	3	28731810	G	A	0.562	0.0226(0.0038)	[95]
770	—	rs247975	3	173107443	C	T	0.562	0.0254(0.0038)	[95]
771	MDGA2	rs723355	14	47304091	G	A	0.562	0.0237(0.0039)	[95]
772	—	–	7	15064896	G	T	0.565	0.101(0.013)	[95]
773	GALNT3	rs13406280	2	166610827	C	T	0.566	0.0269(0.0039)	[95]
774	PRKD1	rs12433335	14	30086481	C	T	0.568	–0.0213(0.0038)	[95]
775	JAZF1	rs860262	7	28194397	C	A	0.568	0.0747(0.0039)	[95]
776	TMEM219	rs8054556	16	29958216	G	A	0.570	–0.0317(0.0039)	[95]
777	AC007796.1	rs2867570	19	31865946	G	A	0.572	0.026(0.0039)	[95]
778	DNM3	rs7546252	1	172368310	G	A	0.573	–0.0262(0.0041)	[95]
779	TTN	rs6715901	2	179650954	G	A	0.573	0.023(0.004)	[95]
780	ZNF236	rs6565922	18	74558999	C	T	0.575	–0.0279(0.0039)	[95]
781	AP003774.1	rs1662185	11	64100776	G	A	0.576	–0.0226(0.0041)	[95]
782	—	rs4397977	13	41688401	G	A	0.576	–0.0283(0.0042)	[95]
783	MAGI2	rs3779272	7	77828991	T	A	0.578	0.0213(0.0038)	[95]
784	—	rs2732469	12	48712932	T	A	0.584	0.0316(0.0042)	[95]
785	MAFF	rs4820323	22	38599767	G	C	0.584	0.0214(0.0039)	[95]
786	C14orf166B	rs2056857	14	77300863	C	T	0.589	0.0256(0.0039)	[95]
787	SLCO4A1	rs1815591	20	61277014	T	A	0.593	–0.0313(0.0041)	[95]
788	FAM212B-AS1	rs197374	1	112289983	C	T	0.593	–0.0224(0.0039)	[95]
789	—	rs8188241	5	46204748	G	A	0.596	0.0232(0.0041)	[95]
790	—	rs7029718	9	23358495	G	A	0.596	–0.0273(0.0039)	[95]
791	GBA2	rs1570247	9	35749014	G	A	0.598	0.0244(0.0039)	[95]
792	RP11-422J15.1	rs2952858	4	130786346	G	A	0.599	–0.0237(0.0041)	[95]
793	RP11-172F10.1	rs9958640	18	4845027	G	A	0.601	–0.0236(0.0042)	[95]
794	—	rs4294149	8	135775546	C	T	0.603	–0.0217(0.0039)	[95]
795	—	rs4942883	13	50431987	C	A	0.605	0.0306(0.0053)	[95]
796	PARP8	rs152839	5	50145266	C	T	0.606	0.0281(0.0039)	[95]
797	HMBS	rs7127212	11	118953202	C	T	0.607	–0.0227(0.0041)	[95]
798	—	rs654629	9	85312075	G	C	0.608	0.0266(0.0039)	[95]
799	TRPS1	rs3802219	8	116565365	C	T	0.608	–0.0357(0.0039)	[95]
800	RP11-252C15.1	rs12056338	8	12643055	G	T	0.609	–0.0251(0.004)	[95]
801	—	rs853866	3	71648868	T	A	0.611	0.0244(0.0044)	[95]
802	*SPIN2A;FAAH2*	–	X	56902211	A	T	0.612	–0.069(0.01)	[95]
803	CWH43	rs2605281	4	49067323	G	A	0.613	–0.0283(0.0041)	[95]

804	ZNF799	rs7246440	19	12505873	G	A	0.620	0.0299(0.0043)	[95]
805	RP4-723E3.1	rs4809906	20	51033681	G	A	0.621	0.0345(0.004)	[95]
806	PEPD	rs4805881	19	33896432	C	A	0.621	−0.0379(0.0039)	[95]
807	TBCE	rs10737818	1	235542023	G	A	0.622	0.0352(0.0052)	[95]
808	RN7SL836P	rs8107527	19	46158417	G	A	0.625	−0.0542(0.004)	[95]
809	JMY	rs2591392	5	78546293	G	A	0.625	0.0306(0.0039)	[95]
810	NFATC2	rs6021276	20	50155386	C	T	0.626	−0.0283(0.004)	[95]
811	KCNH7	rs305686	2	163623932	C	T	0.627	0.0294(0.0053)	[95]
812	HSF1	rs13268508	8	145525277	C	T	0.628	−0.0376(0.0041)	[95]
813	CNTNAP2	rs1922879	7	147658539	G	A	0.629	0.023(0.0041)	[95]
814	HOXC6	rs12422600	12	54429385	G	A	0.638	0.024(0.004)	[95]
815	—	rs1470560	3	35670150	G	A	0.643	−0.0245(0.004)	[95]
816	SIDT1	rs11929640	3	113288430	G	A	0.645	−0.0245(0.0042)	[95]
817	—	rs11078916	17	37746307	C	T	0.647	−0.0326(0.0042)	[95]
818	RP11-282I1.1	rs705145	10	125226178	C	A	0.648	−0.0234(0.0039)	[95]
819	IGF2BP2	rs9859406	3	185534482	G	A	0.648	−0.1117(0.004)	[95]
820	LINC00094	rs379417	9	136890704	G	A	0.649	−0.0278(0.0042)	[95]
821	TRIM66	rs7941510	11	8677063	C	A	0.649	0.0353(0.0042)	[95]
822	HIST1H4E	rs9358912	6	26211146	G	T	0.651	0.0249(0.0045)	[95]
823	—	rs4788815	16	71634811	T	A	0.652	0.0231(0.004)	[95]
824	APIP	rs2956092	11	34908780	C	T	0.653	−0.0254(0.004)	[95]
825	UNC5C	rs3755879	4	96114385	G	A	0.656	−0.0273(0.0042)	[95]
826	BIN3	rs6558173	8	22492103	G	T	0.656	−0.0245(0.004)	[95]
827	GCDH	rs9384	19	13010643	G	T	0.657	0.0404(0.0041)	[95]
828	—	rs3122231	10	44027356	C	T	0.659	0.0271(0.0044)	[95]
829	WDR7	rs10048404	18	54578482	C	T	0.660	0.0313(0.0054)	[95]
830	EHHADH–AS1	rs61579137	3	184882015	G	A	0.660	−0.0309(0.0047)	[95]
831	—	rs10745460	12	88338461	T	A	0.66	0.079(0.014)	[95]
832	SLIT2	rs7664347	4	20265535	C	T	0.660	−0.0234(0.0041)	[95]
833	RNU2–43P	rs620191	10	103065789	G	T	0.664	−0.0234(0.0041)	[95]
834	—	rs10993072	9	96915002	C	T	0.665	−0.0315(0.0041)	[95]
835	ETAA1	rs4671799	2	67622243	G	A	0.667	−0.0262(0.004)	[95]
836	CDH7	rs2032217	18	63426979	G	A	0.667	−0.0268(0.004)	[95]
837	—	rs12825669	12	106288445	G	A	0.667	0.0226(0.0041)	[95]
838	—	rs7274134	20	22428284	C	T	0.670	0.0247(0.0041)	[95]
839	C12orf65	rs10773000	12	123736084	G	T	0.672	0.034(0.0041)	[95]
840	—	rs9872347	3	195831237	C	T	0.674	0.0318(0.0042)	[95]
841	ZBTB26	rs10818763	9	125689694	C	T	0.676	0.0358(0.0051)	[95]
842	POU5F1	rs3130931	6	31134888	C	T	0.677	0.0482(0.0041)	[95]
843	ATP2A1	rs8056890	16	28897452	G	A	0.678	−0.0295(0.0042)	[95]
844	RP11–400F19.6	rs676387	17	40706273	C	A	0.681	−0.0416(0.0041)	[95]
845	PTPN9	rs6495182	15	75814388	C	T	0.685	0.0405(0.0042)	[95]
846	ADAMTS9–AS2	rs66815886	3	64703394	G	T	0.688	0.04(0.0042)	[95]
847	C18orf8	rs303760	18	21083738	C	T	0.689	−0.0334(0.0044)	[95]
848	TOM1	rs138771	22	35705359	G	A	0.690	−0.0259(0.0044)	[95]
849	C15orf52	rs4923864	15	40634717	G	A	0.691	0.0568(0.0061)	[95]
850	CCM2	rs3735491	7	45116468	C	A	0.692	−0.025(0.0043)	[95]
851	IGF1R	rs59646751	15	99276521	G	T	0.693	−0.0241(0.0041)	[95]
852	HEATR5B	rs77424687	2	37204168	C	T	0.696	0.0274(0.0046)	[95]
853	EIF2S2	rs6059662	20	32675727	G	A	0.696	0.0369(0.0043)	[95]

(*continued*)

Table 12.2 (*Continued*)

slno	Nearest gene (*=BMI adjusted)	Index variant	Chromosome	Position (Build 37 bp)	Risk allele	Other allele	RAF (%)	OR (95% CI)/ beta (se)#	Reference
854	STK35	rs6137042	20	2100095	G	A	0.697	0.0263(0.0047)	[95]
855	RASGRP1	rs8043085	15	38828140	G	T	0.698	–0.0407(0.0042)	[95]
856	PRC1	rs2290203	15	91512067	G	A	0.700	–0.0506(0.0043)	[95]
857	NLGN1	rs59489841	3	173710695	C	T	0.702	0.0235(0.0042)	[95]
858	MTOR	rs7554251	1	11317932	C	T	0.702	0.0297(0.0045)	[95]
859	CDKAL1	rs10440833	6	20688121	T	A	0.703	–0.1286(0.0041)	[95]
860	—	rs6835992	4	76496817	G	A	0.705	0.0287(0.0044)	[95]
861	SLC38A9	rs6897117	5	54986775	C	T	0.706	–0.0234(0.0042)	[95]
862	ARVCF	rs2240716	22	19969696	C	T	0.707	–0.0262(0.0042)	[95]
863	COL27A1	rs1431819	9	116943357	G	A	0.708	0.0294(0.0046)	[95]
864	—	rs10758950	9	8290816	T	A	0.708	–0.026(0.0045)	[95]
865	CPNE4	rs9857204	3	131750844	G	A	0.709	–0.0272(0.0043)	[95]
866	AC009518.3	rs12667919	7	131574608	C	A	0.709	–0.0256(0.0047)	[95]
867	CUL1	rs243513	7	148429806	G	A	0.710	0.0232(0.0043)	[95]
868	AUTS2	rs6975279	7	69649683	C	A	0.712	–0.0431(0.0042)	[95]
869	SHQ1	rs9814945	3	72803590	C	T	0.713	–0.0316(0.0048)	[95]
870	ARNTL	rs10766076	11	13340710	T	A	0.714	0.026(0.0043)	[95]
871	FAM46C	rs2282456	1	118169463	G	A	0.715	–0.0351(0.0042)	[95]
872	HDAC9	rs583769	7	18331915	G	A	0.716	–0.0307(0.0043)	[95]
873	RP11–380I10.3	rs11994255	8	28095939	C	T	0.719	–0.0239(0.0043)	[95]
874	CASR	rs13059382	3	121961461	G	T	0.722	0.0356(0.0059)	[95]
875	NSD1	rs4343858	5	176679407	G	A	0.722	0.0295(0.0045)	[95]
876	ALDH1A2	rs11858759	15	58676821	G	A	0.730	0.0236(0.0043)	[95]
877	IFT52	rs6073143	20	42230695	C	T	0.733	0.0304(0.0044)	[95]
878	TRAF3	rs4906272	14	103376031	C	T	0.733	–0.0299(0.0046)	[95]
879	TEX41	rs12151653	2	145726656	C	T	0.735	–0.0267(0.0043)	[95]
880	—	rs11173646	12	61250814	T	A	0.736	–0.0285(0.0047)	[95]
881	RPSAP52	rs2257883	12	66216162	G	A	0.736	–0.071(0.0049)	[95]
882	RP11–17A4.1	rs3887059	8	57496064	G	A	0.736	–0.0295(0.0043)	[95]
883	—	rs9472139	6	43813711	G	C	0.740	–0.0376(0.0044)	[95]
884	PRDM5	rs4833687	4	121765788	C	T	0.742	–0.0267(0.0045)	[95]
885	TMEM161B–AS1	rs6870983	5	87697533	C	T	0.742	0.0287(0.0049)	[95]
886	RAB3C	rs2662390	5	58132702	C	T	0.742	–0.0276(0.0048)	[95]
887	RP11–147C23.1	rs10159026	1	96404462	C	T	0.749	0.0273(0.0046)	[95]
888	SP9	rs12992995	2	175197545	C	A	0.755	0.0272(0.0048)	[95]
889	—	rs7991679	13	58691107	T	A	0.756	0.0274(0.0048)	[95]
890	SLX4	rs8061528	16	3656482	C	T	0.757	–0.0346(0.0045)	[95]
891	RP11–59N23.3	rs11046164	12	21843576	C	T	0.758	0.0289(0.0046)	[95]
892	AMFR	rs111283203	16	56459589	G	C	0.761	–0.0257(0.0047)	[95]
893	—	rs38221	7	15926228	C	T	0.764	–0.0286(0.0047)	[95]
894	KDM3A	rs4832290	2	86707504	C	T	0.765	–0.0267(0.0049)	[95]
895	NRXN3	rs7156625	14	79942647	G	A	0.766	–0.053(0.0049)	[95]
896	—	rs12856169	13	31017268	G	A	0.772	0.0364(0.0061)	[95]
897	—	rs4658234	1	92048779	G	T	0.772	–0.0295(0.0051)	[95]
898	—	rs1650505	5	158029734	G	A	0.772	–0.0409(0.0045)	[95]
899	LIN7A	rs11114650	12	81309262	G	C	0.776	–0.0447(0.0075)	[95]
900	TCF7L2	rs35011184	10	114749734	G	A	0.780	–0.2508(0.005)	[95]

901	MGAT1	rs6885157	5	180226516	G	T	0.783	0.0372(0.0068)	[95]
902	RP11–85K15.2	rs712315	14	35409701	T	A	0.783	0.0282(0.0051)	[95]
903	LARP1B	rs4834232	4	129024273	C	T	0.787	–0.0272(0.0047)	[95]
904	—	rs12192275	6	127412728	G	A	0.789	0.0482(0.005)	[95]
905	NTAN1	rs9927842	16	15153717	C	T	0.789	–0.0307(0.005)	[95]
906	MED23	rs2608953	6	131926334	C	T	0.789	–0.0348(0.005)	[95]
907	FSD2	rs36111056	15	83461873	G	A	0.792	0.0303(0.0053)	[95]
908	CHD4	rs7316626	12	6691452	G	A	0.797	–0.0322(0.0054)	[95]
909	NOS1	rs884847	12	117723613	G	A	0.803	–0.0293(0.005)	[95]
910	KDM4B	rs12185519	19	4967739	C	T	0.808	–0.036(0.0054)	[95]
911	EML6	rs5010712	2	55157914	G	A	0.812	0.03(0.0051)	[95]
912	PCBD1	rs827237	10	72648336	C	T	0.813	–0.0294(0.0053)	[95]
913	AZIN1	rs2679745	8	103876325	G	A	0.814	0.0278(0.0049)	[95]
914	HPSE2	rs524903	10	100421841	G	A	0.816	0.0428(0.0067)	[95]
915	—	rs11172254	12	57968738	G	A	0.817	0.097(0.017)	[95]
916	—	rs13288108	9	29089437	C	A	0.822	0.0274(0.005)	[95]
917	RP5–1024C24.1	rs10835690	11	30620262	T	A	0.822	–0.029(0.0052)	[95]
918	—	rs7227272	18	36746623	G	A	0.823	0.0408(0.0056)	[95]
919	VPS53	rs11870735	17	481604	C	T	0.824	–0.0314(0.0054)	[95]
920	KSR2	rs79310463	12	118406696	C	T	0.826	–0.05(0.0053)	[95]
921	GCK	rs730497	7	44223721	G	A	0.828	–0.0552(0.005)	[95]
922	RPL13	rs12932337	16	89630630	C	T	0.830	–0.034(0.0052)	[95]
923	—	rs57286125	13	33557644	G	C	0.832	–0.0609(0.0051)	[95]
924	RP3–523E19.2	rs9370243	6	53789830	G	T	0.834	–0.0394(0.0061)	[95]
925	ZNF800	rs17866443	7	127058953	C	A	0.839	–0.2003(0.0139)	[95]
926	—	rs10188334	2	653874	C	T	0.841	0.0544(0.0053)	[95]
927	TCF12	rs28490139	15	57369850	G	A	0.842	0.0375(0.0053)	[95]
928	SLC1A2	rs58090211	11	35433712	C	A	0.843	0.0539(0.0091)	[95]
929	SETD5	rs3872707	3	9514016	G	A	0.844	–0.037(0.0054)	[95]
930	TCF3	rs4807125	19	1646712	C	T	0.848	–0.0326(0.0059)	[95]
931	FCGRT	rs142385484	19	50016759	C	T	0.852	0.0336(0.006)	[95]
932	*TENM1*	–	X	124390172	T	C	0.853	–0.075(0.013)	[95]
933	PPT2–EGFL8	rs3130283	6	32138545	C	A	0.853	0.0617(0.0057)	[95]
934	RP1–90K10.4	rs72846863	6	36911274	G	A	0.856	0.0335(0.0061)	[95]
935	FOXK1	rs62452060	7	4683572	G	A	0.864	–0.0354(0.0059)	[95]
936	TMEM87B	rs74677818	2	112823114	C	T	0.865	–0.0357(0.006)	[95]
937	RP11–25I15.2	rs11181613	12	43046449	C	A	0.869	0.0418(0.006)	[95]
938	JMJD1C	rs111765639	10	64970928	G	A	0.876	0.0581(0.0084)	[95]
939	RP11–686O6.2	rs6714523	2	203235139	G	A	0.881	–0.0401(0.0061)	[95]
940	SLC39A11	rs61736066	17	70645032	G	A	0.881	0.0421(0.0064)	[95]
941	—	rs506597	7	100313420	G	A	0.881	0.041(0.0064)	[95]
942	—	rs7315028	12	38710523	G	A	0.882	0.124(0.022)	[95]
943	SUGCT	rs17439448	7	40816653	C	T	0.884	–0.0393(0.0067)	[95]
944	SBF2	rs76789970	11	9856015	C	T	0.887	–0.0387(0.006)	[95]
945	LEPR	rs10889560	1	65989878	C	A	0.889	–0.0376(0.0063)	[95]
946	EP400	rs11830241	12	132544643	C	T	0.901	–0.0411(0.0072)	[95]
947	PDE3A	rs7134150	12	20591332	G	A	0.901	–0.0443(0.007)	[95]
948	RP11–159G9.5	rs73146095	3	88130136	C	T	0.902	0.0406(0.007)	[95]
949	—	rs59020573	1	33196120	G	A	0.908	–0.0503(0.0088)	[95]

(*continued*)

Table 12.2 (*Continued*)

slno	Nearest gene (*=BMI adjusted)	Index variant	Chromosome	Position (Build 37 bp)	Risk allele	Other allele	RAF (%)	OR (95% CI)/ beta (se)#	Reference
950	—	rs73167517	5	87102981	G	T	0.913	–0.0411(0.0072)	[95]
951	SMARCC1	rs62262091	3	47693664	C	T	0.913	–0.0538(0.0084)	[95]
952	—	rs73239895	17	6953558	C	T	0.914	–0.0869(0.011)	[95]
953	RP11–1102P16.1	rs10101067	8	72407374	G	C	0.914	–0.0391(0.0069)	[95]
954	CTA–85E5.10	rs56392746	22	30451688	G	A	0.917	0.0579(0.0076)	[95]
955	—	rs10305420	6	39016636	C	T	0.92	0.142(0.025)	[95]
956	UNC79	rs11848361	14	94039845	G	A	0.921	0.0478(0.0085)	[95]
957	ARID5B	rs146716733	10	63717113	C	T	0.921	0.0451(0.0079)	[95]
958	SLC39A8	rs13107325	4	103188709	C	T	0.927	–0.0473(0.0086)	[95]
959	SV2A	rs72692804	1	149891028	G	C	0.927	0.0532(0.0084)	[95]
960	CTRB2	rs72802365	16	75246035	G	C	0.928	0.1074(0.008)	[95]
961	—	rs35164294	6	130265266	G	T	0.929	–0.0525(0.0092)	[95]
962	USP44	rs11108094	12	95928113	C	A	0.934	–0.0571(0.0088)	[95]
963	ERN1	rs57767539	17	62203059	G	A	0.936	–0.0622(0.0091)	[95]
964	MEG3	rs112324411	14	101258584	C	T	0.938	0.0729(0.0103)	[95]
965	—	rs60461843	8	118166327	T	A	0.939	0.172(0.028)	[95]
966	NELL1	rs16907058	11	20952237	G	A	0.941	–0.0461(0.0084)	[95]
967	HS6ST3	rs61967710	13	97176585	G	A	0.941	–0.0554(0.0099)	[95]
968	—	rs16881572	6	51413013	G	A	0.945	–0.0681(0.011)	[95]
969	RP11–42A4.1	rs117233795	4	85297954	C	T	0.956	0.1426(0.0201)	[95]
970	KIF3C	rs72803684	2	26192802	C	T	0.956	–0.0666(0.0115)	[95]
971	MYO5C	rs149336329	15	52587740	G	T	0.957	0.0869(0.01)	[95]
972	PCGF3	rs73221116	4	720681	G	A	0.958	–0.0955(0.0106)	[95]
973	—	rs12494424	3	70520917	G	C	0.958	–0.0656(0.0117)	[95]
974	QSER1	rs62618693	11	32956492	C	T	0.958	0.0819(0.0111)	[95]
975	KCNJ12	rs117642733	17	21284910	C	T	0.958	–0.0762(0.0133)	[95]
976	AFF3	rs34506349	2	100598726	G	A	0.961	0.0665(0.0116)	[95]
977	USP49	rs2031847	6	41864441	G	C	0.967	–0.0752(0.0133)	[95]
978	*MAP3K15*	–	X	19497290	A	G	0.968	0.131(0.023)	[95]
979	RP11–624L4.1	rs148106383	15	39712286	C	T	0.975	–0.0928(0.0156)	[95]
980	C1orf172	rs79598313	1	27284913	C	T	0.977	–0.0867(0.0148)	[95]
981	ZNF76	rs33959228	6	35259397	C	T	0.979	0.0915(0.0155)	[95]
982	ACVR1C	rs149447188	2	158449081	C	T	0.991	–0.1702(0.0267)	[96]
983	GLIS3	rs4237150	9	4290085	G	C	0.571	–0.0433(0.0037)	[94,95]
984	ZBED3–AS1, ZBED3	rs7732130	5	76435004	G	A	0.295	0.0554(0.0047)	[94,95]
985	SLC2A2	rs8192675	3	170724883	C	T	0.317	–0.0452(0.0042)	[94,95]
986	ZZEF1	rs8071043	17	3988451	C	T	0.332	0.0465(0.0041)	[94,95]
987	*FXYD6–FXYD2*	rs529623	11	117693255	C	T	0.496	–0.0224(0.0038)	[94,95]
988	SLC12A8	rs9873519	3	124921457	C	T	0.529	–0.0373(0.0038)	[94,95]
989	PURG	rs2725370	8	30852826	C	T	0.713	–0.0319(0.0046)	[94,95]
990	MOB1B	rs7674402	4	71835822	G	A	0.771	–0.0523(0.0064)	[94,95]
991	*OLFM4*	rs9568868	13	54107583	G	T	0.840	–0.035(0.0053)	[94,95]
992	DEPDC5, YWHAH	rs75307421	22	32203334	G	A	0.969	–0.0737(0.0132)	[94,95]
993	*CCNQ; DUSP9; G6PD*		X	153882606	C	G	0.026	–0.486(0.026)	[95]

BMI, body mass index; CI, confidence interval; OR, odds ratio; RAF, risk allele frequency.

Table 12.3 Example of genetic loci associated with glycaemic traits.

N	SNPs	GENE/ nearest gene	Gene location	Chr	Effect allele	Other allele	Effect	Trait	References
1	rs9727115	SNX7	Intron	1	G	A	0.0133	Fasting proinsulin levels adjusted for fasting glucose	[96]
2	rs2785980	LYPLAL1	Intergenic	1	T	C	0.017	Fasting insulin	[97]
3	rs4675095	IRS1	Intron	2	A	T	–0.006/–002	Fasting glucose/HOMA-IR	[98]
4	rs2943634	IRS1	Intergenic	2	C	A	0.025	Fasting insulin, CAD	[97]
5	rs1371614	DPYSL5	Intron	2	T	C	0.022	Fasting glucose	[97]
6	rs11920090	SLC2A2	Intron	3	T	A	0.02	Fasting glucose/HOMA B/HbA_{1C}	[98]
7	rs17046216	MSMO1	Intron	4	A	T	0.18; 0.19	Fasting insulin; insulin resistance	[99]
8	rs4691380	PDGFC	Intron	4	C	T	0.021	Fasting insulin	[97]
9	rs6235	PCSK1	Coding – missense	5	G	C	0.0394/–0.014	Fasting proinsulin levels/fasting glucose	[96]
10	rs13179048	PCSK1	Intergenic	5	C	A	0.018	Fasting glucose	[97]
11	rs4646949	TAF11	NearGene-3	6	T	G	0.020	Fasting insulin	[97]
12	rs6943153	GRB10	Intron	7	C	T	0.0154	Fasting glucose, fasting insulin	[13]
13	rs4841132	PPP1R3B	Intergenic	8	A	G	0.030	Fasting glucose	[97]
14	rs7077836	TCERG1L	Intergenic	10	T	C	0.28; 0.34	Fasting insulin; insulin resistance	[99]
15	rs7944584	MADD	Intron	11	A	T	0.021	Fasting proinsulin/fasting glucose/HOMA B	[98]
16	rs10838687	MADD	Intron	11	T	G	0.0253	Fasting proinsulin levels	[96]
17	rs1483121	OR4S1	Intergenic	11	G	A	0.015	Fasting glucose	[97]
18	rs2074356	HECTD4/C12orf51	Intron	12				1 h plasma glucose	[100]
19	rs2293941	PDX1 – AS1	Intron	13	A	G	0.016	Fasting glucose	[97]
20	rs17271305	VPS13C	Intron	15	G	A	0.07	2 h glucose/2 h insulin, adjusted for 2 h glucose	[101]
21	rs1549318	LARP6	Intergenic	15	T	C	0.0192	Fasting proinsulin levels	[96]
22	rs4790333	SGSM2	Intron	17	T	C	0.0154	Fasting proinsulin levels	[96]
23	rs10423928	GIPR	Intron	19	A	T		2 h glucose/insulinogenic index/AUCins/gluc/2 h insulin, adjusted for 2 h glucose/type 2 diabetes	[101]
24	rs6048205	FOXA2/LINC00261	Intergenic/ nearGene-5	20	A	G	0.029	Fasting glucose	[97]

AUC, area under the curve; CAD, coronary artery disease; HbA_{1C}, glycated haemoglobin; HOMA B, homeostatic model 2 of assessment for insulin secretion; HOMA-IR, homeostatic model 2 of assessment for insulin resistance; SNPs, single-nucleotide polymosphisms.

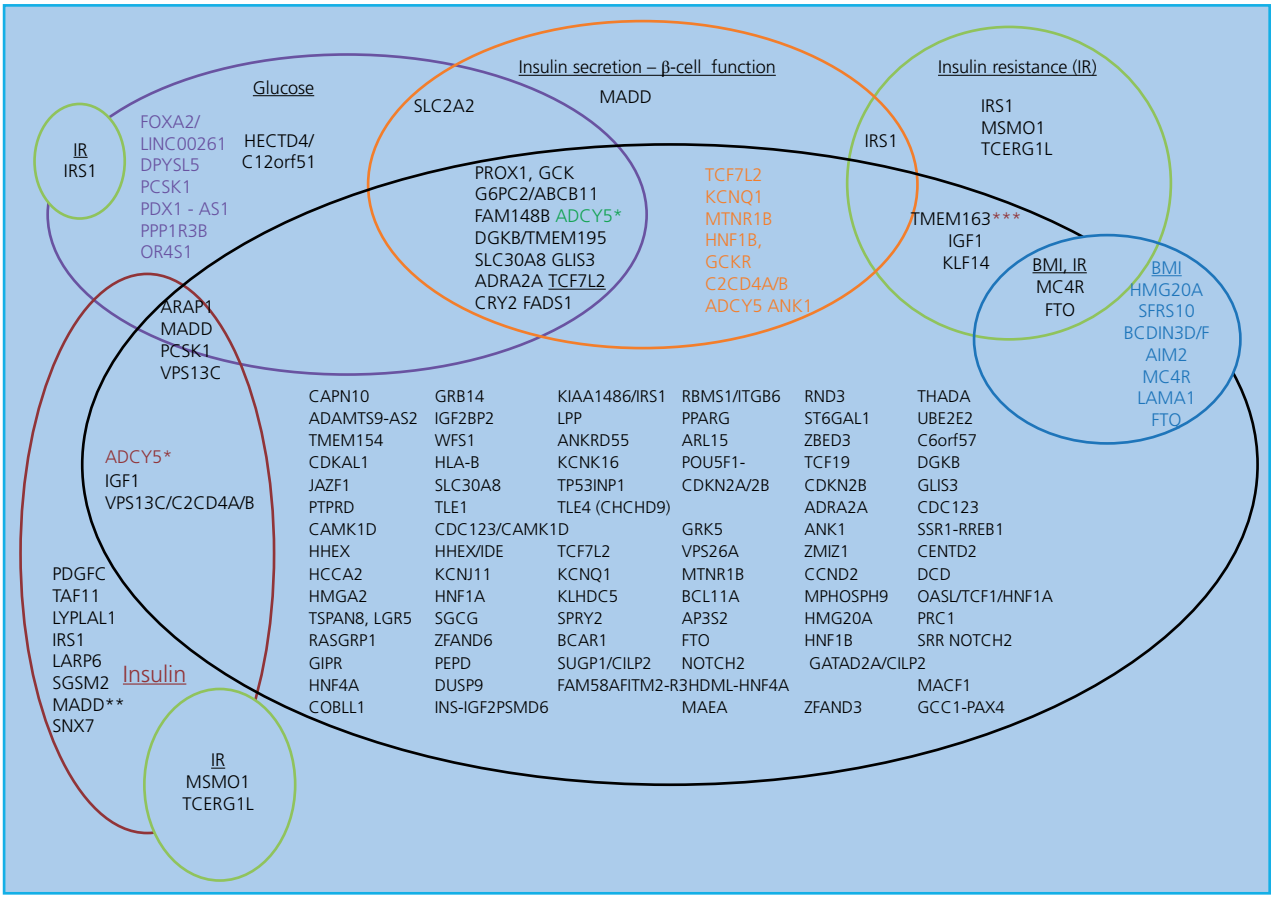

Figure 12.2 Type 2 diabetes– and glycaemic trait–associated variants. The variants are represented by gene names here, which could indicate that the location is present either in the gene or in the vicinity of the gene. The black circle represents type 2 diabetes, and the gene names in black in this represent variants only associated with type 2 diabetes. The overlapping circles indicate additional reporting associations for that variant, e.g. *TCF7L2*, *KCNQ1*, and *MTNR1B* are associated with type 2 diabetes and also with β-cell dysfunction. *An *ADCY5* variant is associated with two-hour insulin adjusted for two-hour glucose, two-hour glucose/type 2 diabetes (in brown). **MADD variants are associated with fasting proinsulin, fasting glucose, and HOMA-B (homeostatic model 2 of assessment for insulin secretion). ***Variants in *TMEM163* are also associated with fasting insulin, and *TCF7L2* associated with fasting and two-hour glucose.

from Greenland revealed a nonsense p.Arg684Ter variant (allele frequency of 17%) in *TBC1D4* associated with higher concentrations of two-hour glucose and serum insulin [109]. Whole-exome sequencing in a Latino population revealed a rare missense variant in *HNF1A* (c.1522G>A [p.E508K]) that was associated with type 2 diabetes prevalence [108]. Additionally, rare variants associated with glycaemic traits were discovered through exome sequencing of 9717 individuals from the METSIM study, Finland [106] (Table 12.4).

Protective variants

The average type 2 diabetes risk variant frequency in the general population is 54%, which raises the question of whether type 2 diabetes is the default condition. If so, then does carrying protective variants makes a difference in disease susceptibility? Studies have been performed to address this question by including controls that, despite having a cluster of risk factors for type 2 diabetes, have escaped the disease. A rare (0.66%) loss-of-function mutation (R138X) was detected in the *SLC30A8* gene in the Botnia region of Finland and was subsequently replicated in a massive effort applying the Exome chip to >150 000 individuals from other European countries. Also, the DeCode group identified another loss-of-function mutation, a frameshift mutation that also was enriched in Icelandic people without diabetes. The *SLC30A8* gene encodes the islet zinc transporter 8 with a putative effect on insulin secretion. Notably, a common variant in the same gene increases susceptibility to type 2 diabetes, whereas zinc transporter 8 autoantibodies predispose to type 1 diabetes.

Collectively, carriers of these protein-truncating mutations have a 65% lower risk of type 2 diabetes [107]. Other studies based on Icelandic, Danish, and Iranian populations identified a low-frequency variant in *CCND2* that reduced type 2 diabetes risk by half [105]. Moreover, variants in *TCF2* are protective against type 2 diabetes [110]. It is also likely that the more recent such variants that are only a few generations old segregate in families and could be detected though sequencing in families (Table 12.4).

Gene–gene and gene–environment interactions

Gene–gene interactions, or epistasis, have been suggested as a possible explanation for difficulties in replicating genetic associations in complex diseases [111]. The standard statistical methods used in association studies are usually limited to analysis of single marker effects and thereby do not account for interactions between

Table 12.4 Rare risk and protective loci associated with type 2 diabetes and glycaemic trait.

N	SNPs	Gene/nearest gene	Gene location	Chr	References
1	rs35658696	*PAM*	Coding – missense	5	[106]
2	rs78408340	*PAM*	Coding – missense	5	[106]
3	rs36046591	*PPIP5K2*	Coding – missense	5	[106]
4	p.Lys34Serfs*50	*SLC30A8*	Coding – missense	8	[107]
5	p.Arg138*	*SLC30A8*	Coding – missense	8	[107]
6	rs3824420	*KANK1*	Coding – missense	9	[106]
7	rs505922	*ABO*	Intronic	9	[106]
8	rs60980157	*GPSM1*	Coding – missense	9	[106]
9	p.Leu5Val (20)	*ATG13*	Coding – missense	11	[106]
10	p.Ile131Val (1)	*ATG13*	Coding – missense	11	[106]
11	p.Gln249Pro (3)	*ATG13*	Coding – missense	11	[106]
12	p.Arg392Trp (1)	*ATG13*	Coding – missense	11	[106]
13	p.Leu427Gln (3)	*ATG13*	Coding – missense	11	[106]
14	p.Gly434Arg (488)	*ATG13*	Coding – missense	11	[106]
15	p.X406Gly (200)	*ATG13*	Coding – missense	11	[106]
16	rs35233100	*MADD*	Coding – missense	11	[106]
17	p.Arg279Cys (324)	*TBC1D30*	Coding – missense	12	[106]
18	p.Pro746Leu (427)	*TBC1D30*	Coding – missense	12	[106]
19	c.1522G>A [p.E508K]	*HNF1A*	Coding – missense	12	[108]
20	rs76895963	*CCND2*	Intergenic	12	[105]
21	rs75615236	*CCND2*	Intergenic	12	[105]
22	rs150781447	*TBC1D30*	Coding – missense	12	[106]
23	rs2650000	*HNF1A*	Intergenic	12	[106]
24	Chr. 13: g.27396636delT	*PDX1*	Coding – missense	13	[107]
25	p.Tyr416Cys (78)	*SGSM2*	Coding – missense	17	[106]
26	p.Thr789Pro (3),	*SGSM2*	Coding – missense	17	[106]
27	p.Val996Ile (236)	*SGSM2*	Coding – missense	17	[106]
28	rs61741902	*SGSM2*	Coding – missense	17	[106]

Chr, chromosome.

markers. Previous attempts to study epistasis in complex diseases have focused on interactions between candidate regions [112,113]. However, the recent abundance of GWAS has made a comprehensive search across the genome more feasible. Some studies have attempted to account for epistasis in GWAS using a two-step approach in which significant SNPs are tested against each other or against all other SNPs in the study, with variable results [114,115]. The main problem when studying epistasis is power, since interaction between loci with modest effects is difficult to detect without extremely large sample sizes. However, some studies have pointed at novel tests to increase power [116]. Thorough studies in diabetes addressing epistasis using this approach are missing. A recent paper by Eric Lander et al. provided compelling evidence that gene–gene interaction can also contribute to missing heritability by causing *phantom heritability*, which inflates the estimated narrow sense heritability of the trait [117].

Gene–environment interactions are equally difficult to study, but are likely to play an important role in type 2 diabetes development. The epidemic of type 2 diabetes only dates back 50 years, and it is quite obvious that during this period only the environment, not the genes, has changed. However, our genetic architecture determines our response to the environment. Genetic variants could affect specific metabolic processes to make an individual more susceptible to the harmful effects of a poor diet, but also personality traits that make an individual more or less likely to overconsume and live a sedentary lifestyle. It will, however, be a formidable task to identify the environmental triggers for most of the genetic variants increasing susceptibility to diabetes, as this will require very large studies with precise information on diet, exercise, energy expenditure, and so on.

Parent-of-origin effects

The risk of type 2 diabetes in offspring is greater if the mother has type 2 diabetes compared to if the father is affected, in contrast to type 1 diabetes, where the risk of type 1 diabetes in offspring is greater if the father is affected [118,119]. Sex-specific parental effects have been reported for insulin response to an oral glucose load, with male offspring of women with diabetes showing the lowest insulin values, as well as influencing high-density lipoprotein (HDL) concentrations [118]. One potential explanation for this could be preferential parental-specific transmissions of risk alleles to offspring, which is often associated with DNA methylation and imprinting. Epigenetic modifications have the potential to be stable and heritable across cell divisions and manifest as parent-of-origin effects [120,121]. Insulin was the first gene reported to show parent-of-origin effects. The paternally transmitted class III alleles of the variable-number tandem repeat (VNTR) region upstream of the insulin gene (INS–VNTR) showed an association with type 2 diabetes [122]. Interestingly, class III alleles (one of the two main classes of INS–VNTR allele length, with 141–209 repeats) were also associated with increased length and weight at birth [123] and were protective against type 1 diabetes compared with type I alleles [124]. A large-scale family-based study in

Iceland determined that variants in *KCNQ1* and *KLF14* show stronger effects on type 2 diabetes when the risk allele is transmitted from the mother than from the father [125, 126] and were replicated in later studies, including our own [127].

The conflict hypothesis suggests that imprinting arose due to a genomic *tug of war* between mothers and fathers over the use of maternal resources in the fetus. The paternal imprinting maximizes the utilization of intrauterine resources by the offspring, which would increase their evolutionary fitness, whereas the maternal imprinting tries to minimize this to conserve it for her future offspring [128]. Conversely, the co-adaptation hypothesis suggests that imprinted genes coevolve to optimize parental care of offspring. While there is insufficient evidence to support either theory, nevertheless the significant role of imprinting in defining paternal and maternal effects has been consistently established [129].

The intrauterine environment plays a significant role in determining fetal programming. Poor maternal nutrition can affect fetal growth and produce permanent changes in glucose–insulin metabolism, and often results in low birth weight [130]. This can induce permanent changes in metabolism and affect chronic disease susceptibility, as proposed by the developmental origins of health and disease hypothesis [131]. If this intrauterine programming results in a reduced β-cell mass, it could predispose to diabetes later in life when the insulin requirements increase as a consequence of obesity, resulting in insulin resistance. *KCNQ1* could represent an example of fetal programming wherein the maternally expressed gene was mono-allelically expressed in fetal tissues and biallelically expressed in adult tissues [132].

Dissection of genetic parent-of-origin effects requires genotype data from families and only heterozygous parents are informative, yielding reduced power for relatively rare variants. However, long-range phasing and imputation methods allow for predicting genotypes with great likelihood, thus making this a valuable method to find *surrogate* parents, even if DNA exists from only a few family members. When the paternal and maternal alleles have effects in opposite directions, for instance a situation where the maternal allele could confer risk while the paternal allele could be protective, such an association would be almost impossible to detect in a traditional case–control GWAS. However, novel parent-of-origin detection methods allow detection of imprinting effects from differences in the phenotypic variance of heterozygotes in very large case–control studies [133]. Parent-of-origin effects could explain a large portion of the missing heritability and must be taken into consideration in investigations of genetic type 2 diabetes susceptibility.

Epigenetics

The environment can also influence the expression of the genome, and ultimately the phenotype, via the epigenome. Even though the DNA sequence is not changed, the phenotype is altered by epigenetic modifications of gene expression by mechanisms including methylation of DNA, post-translational modification of histones, or activation of microRNAs. Changes to the phenotype can be at the level of the cell, tissue, or whole organism.

It is tempting to speculate that environmental factors such as diet and exercise can change the level of DNA methylation and thereby cause changes in gene expression, but evidence that DNA methylation contributes to the increase in type 2 diabetes is still lacking. Epigenetic mechanisms may, however, play a role in progression of the disease by inducing glucotoxicity in islets and predispose to diabetes-related complications [134]. Elevated glucose is a prerequisite for this condition and cells can memorize changes in glucose concentrations. For example, two large studies, the UK Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT), showed that initial good metabolic management was associated with reduced frequency of diabetes complications decades later. The advanced *metabolic memory* hypothesis suggests that this is because glucose can induce histone modifications in endothelial cells that can be remembered long after (Chapter 42) [135].

Non-coding RNAs – MicroRNAs and LincRNAs

Non-coding RNAs have recently emerged as important regulators of gene expression and function. MicroRNAs (miRNAs) naturally regulate programmes of gene expression. Altered miRNA function contributes to human disease, and manipulation of specific miRNAs is now being explored as a novel therapeutic modality [136]. The efficiency of miRNAs binding to target transcripts depends on both the sequence and the intramolecular structure of the transcript. SNPs can contribute to alterations in the structure of regions flanking them, thereby influencing the accessibility for miRNA binding. Several studies have implicated miRNAs in diabetes and inflammation and common SNPs change the target sequence of miRNAs in several type 2 diabetes susceptibility loci (http://miracle.igib.res.in/dbSMR) [137, 138]. Other forms of non-coding RNAs, such as piRNAs (PIWI-interacting RNAs), snoRNAs (small nucleolar RNAs), lincRNAs (long intergenic non-coding RNAs), and lncRNAs (long non-coding RNAs), might also contribute to the development of diabetes. For example, the CDKN2A/B region on chromosome 9 is associated with type 2 diabetes, as well as cardiovascular disease and a number of other disorders. This region harbours a lincRNA, ANRIL (non-protein coding CDKN2B-AS1 CDKN2B antisense RNA 1), which can potentially modify and explain some of these associations [139].

Difficulties in assigning functions to associated genes

Most identified diabetes loci have not been mechanistically tied to the disease. While loci are commonly referred to by the names of genes located close to them, only a few are close to strong biological candidates, such as the melatonin receptor (*MTNR1B*) and the insulin receptor substrate-1 (*IRS1*). For others, like *TCF7L2* and *GIPR*, the evidence is quite strong that an intronic SNP is the causal SNP. Melatonin receptor 1B (*MTNR1B*) has been associated with both fasting glucose and risk of type 2 diabetes [140–142]. Melatonin works as a chronobiotic factor, adjusting the timing of the biological clock. Its receptors are present in the pancreas and melatonin is proposed to contribute to the nocturnal lowering of insulin in humans. The *MTNR1B* risk genotype is associated with impaired early insulin release to both oral and intravenous glucose and insulin secretion deteriorates over time in the risk allele carriers [140]. The proposed

mechanism by which the *MTNR1B* polymorphism could predispose to type 2 diabetes involves altered expression of *MTNR1B* in pancreatic β cells, leading to decreased cyclic adenosine monophosphate/cyclic guanosine monophosphate (cAMP/cGMP) concentrations via G-proteins and, thereby, impaired insulin secretion.

The insulin receptor substrate 1 (*IRS1*) gene encodes a protein that mediates insulin's control of various cellular processes by transmitting signals from the insulin receptor to intracellular signalling pathways. The C allele of rs2943641 is associated with insulin resistance and increased risk of diabetes. The genetic variant causes reduced basal levels of IRS1 protein and decreased insulin induction of IRS1-associated phosphatidylinositol-3-hydroxykinase activity in human skeletal muscle biopsies [143].

TCF7L2 is a transcription factor playing an important role in the Wnt signalling pathway. The risk allele is associated with a decreased insulinogenic index and a lower disposition index, suggesting a reduced capacity for insulin secretion in relation to insulin sensitivity. Since it was identified as a diabetes gene, it has been shown to be important for several vital functions in the pancreatic islet, including pancreas development, determination of β-cell mass, maintenance of the secretory function of mature β cells, and regulation of insulin production and processing [144, 145].

The incretin hormone glucose-dependent insulinotropic polypeptide (GIP) promotes pancreatic β-cell function by potentiating insulin secretion and β-cell proliferation. The GIP receptor (*GIPR*) locus showed an association with post-prandial insulin levels in a meta-analysis performed by the MAGIC consortium, but was surprisingly not associated with risk of diabetes in the DIAGRAM+ study [12, 101]. The reason seems to be that the same variant results in a decreased body mass index, which neutralizes the effect of the SNP on risk of type 2 diabetes. GIP influences expression of the inflammatory cytokine OPN in islets, which in turn has protective effects on β-cell proliferation and potentially apoptosis [146].

Many of the other identified loci can be subgrouped based on their association with other phenotypes with a key role in type 2 diabetes aetiology. Exploration of the effects of type 2 diabetes–associated variants on glucose and insulin traits in people without diabetes has shown that most of the known loci act through an effect on insulin secretion rather than insulin resistance (Table 12.2) [12, 147–149].

Fasting glucose–raising alleles of the *MADD*, *GIPR*, *GCK*, *FADS*, *DGKB*, *PROX1*, *TCF7L2*, *SLC30A8*, and *C2CD4B* loci have all been associated with either abnormal insulin processing or secretion, whereas *GCKR* and *IGF1* are associated with oral glucose tolerance test–based disposition indices and β-cell function [148]. The DIAGRAM+ consortium observed that three loci (*TCF7L2*, *ARAP1*, and *CDKAL1*) were associated with reduced fasting insulin, also suggestive of β-cell dysfunction, whereas the type 2 diabetes risk alleles at *PPARG*, *FTO*, *IRS1*, and *KLF14* were associated with higher fasting insulin, indicating a primary effect on insulin action [12].

Genotype-based treatment

The *ADRA2A* (adrenergic receptor α2) locus was recently identified as a type 2 diabetes risk locus after first having been positionally mapped in congenic GK rats, where it was associated with impaired insulin granule docking and reduced β-cell exocytosis [147]. Human carriers of the *ADRA2A* risk variant (rs553668) have reduced fasting insulin and decreased insulin secretion as a consequence of increased expression of the ADRA2 receptor in pancreatic islets. It is well known that epinephrine excess can suppress insulin secretion and cause diabetes. The α_{2A}-adrenergic receptor (α_{2A}AR) antagonist yohimbine enhances insulin release *in vitro* in islets from organ donors carrying the risk allele to levels similar to those in non-risk carriers. A randomized clinical study was performed blocking α_{2A}AR pharmacologically to increase insulin secretion in individuals with type 2 diabetes and the rs553668 risk allele. Yohimbine administration enhanced 30-minute insulin and corrected the insulin response and disposition index in the risk group, making secretion similar to individuals carrying the low-risk allele. An insulin secretion defect in individuals carrying the *ADRA2A* risk genotype could be corrected by α_{2A}AR antagonism [150]. This demonstrated the potential application of genetic risk variants to guide therapeutic interventions that target the underlying pathophysiology, one step closer to individualized medicine.

Little common genetic basis for type 1 diabetes and type 2 diabetes

Type 1 diabetes and type 2 diabetes can be considered two extremes of the diabetes spectrum and share a few similarities in manifestation of underlying physiology, including hyperglycaemia, insulin deficiency, and development of complications. However, the genetics of type 1 and type 2 diabetes vastly differ, with very few type 2 diabetes susceptibility loci showing an association with type 1 diabetes. Notable exceptions include the *PPARG* Pro12Ala variant, *MTNR1B*, *HNF1A*, *GLIS3*, 6q22.32, and novel loci near the MHC, which harbour the HLA class II genes associated with about half the type 1 diabetes risk [92, 151–153]. Based on these studies, the mechanisms underlying type 1 and type 2 diabetes appear to be intrinsically distinct. The distribution of type 2 diabetes risk SNPs should be more random in individuals with type 1 diabetes; however, this does not seem to be the case. The strongest type 2 diabetes SNP in the *TCF7L2* gene almost seems to protect from type 1 diabetes. Type 1 diabetes risk variants for *BCAR1*, *GLIS3*, and *RAD51L1* were protective for type 2 diabetes, whereas for those in *C6orf173*, *COBL*, and *C10orf59* the effects were concordant [84]. Also, it has been reported that APOC3 haplotypes increase the risk of type 1 diabetes; however, the same variants increase the risk of type 2 diabetes in lean carriers, while having a protective effect in overweight carriers [154]. Common variants in SLC30A8 are associated with an increased risk of type 2 diabetes, and rare variants with a protective effect [80, 107]. Puzzlingly, SLC30A8 was also found to be a major autoantigen eliciting 60–80% of autoantibodies in people with new-onset type 1 diabetes [155].

Curiously, gene variants associated with type 1 diabetes underwent recent positive selection and have been increasing in prevalence. There is more selection in alleles increasing, rather than decreasing, susceptibility to type 1 diabetes. This is indicative of an evolutionary benefit, wherein these variants were possibly protective against viruses and bacterial infections. However, no such link has been reported for type 2 diabetes risk variants, as could be expected from the thrifty genotype hypothesis [156]. In terms of genetics, type 2 diabetes seems to have more in common with

that of cancer rather than of type 1 diabetes [157]. There may rather be a specific yin–yang relationship between cancer and type 2 diabetes, with too much cell proliferation resulting in cancer and insufficient proliferation of pancreatic islets resulting in type 2 diabetes [157].

LADA is considered an intermediary form between type 1 diabetes and type 2 diabetes. There is much less information available as to the genetic basis of LADA compared to type 1 diabetes and type 2 diabetes. One way to understand this would be to assess to what extent LADA shares genetic similarities with type 1 diabetes and type 2 diabetes. The HLA locus, conferring 50% of the genetic susceptibility to type 1 diabetes, also shows similar associations with LADA, with a few differences. The type 1 diabetes variant *PTPN22* shows a weak association with LADA. Data on the INS class I VNTRs have been inconclusive and associations have been reported with both type 1 diabetes and type 2 diabetes, wherein the short tandem repeat is associated with type 1 diabetes and the long with type 2 diabetes. While several type 1 diabetes–associated variants could be tested for association with LADA, it was not until the discovery of the common variant in the *TCF7L2* gene being strongly associated with type 2 diabetes that the genetic contribution of type 2 diabetes to LADA really could be tested. This variant is clearly associated with LADA and type 2 diabetes, but not with type 1 diabetes. This indicates that LADA is indeed a genetic admixture of both type 1 diabetes and type 2 diabetes. There are more lessons to be learned from differences between type 1 diabetes and type 2 diabetes rather than similarities. Elucidating the genetic heterogeneity of the spectrum of diabetes disorders will help us in understanding the mechanisms underlying the phenotypic heterogeneity of diabetes and would be a step towards individualized therapy.

A holistic view: systems genetics

A restricted focus on the genome through GWAS provides limited insights into the molecular mechanisms driving disease and is akin to a snapshot of the genetics of the disease. To obtain an understanding of disease pathogenesis, it is important to analyse the data from GWAS in the context of complementary follow-up analyses, including DNA methylation and histone modifications, expression profiling under conditions relevant for the disease, related protein analysis, and analysis of genotype–phenotype associations. Global transcriptome profiling in relevant tissues such as pancreas has facilitated identification and cataloguing of a wide array of transcription-based events in the pathogenesis of type 2 diabetes [158]. For example, by combining GWAS information with metabolomics, it has been possible to identify strong associations between SNPs and metabolic reactions that otherwise would have been missed [159]. Network- or pathway-based approaches, including enrichment in pre-defined pathways by for example KEGG [160] (http://www.genome.jp) and Gene Ontology (GO; http://www.geneontology.org), have also been used to identify disease genes for various diseases. Thus, an integrative approach of several data types is likely to discover disease genes that would not be identified using classical GWAS approaches alone. This was also illustrated in a recent studies of human islets identifying novel candidate genes for type 2 diabetes based on expression differences and co-expression with known type 2 diabetes genes as well as protein–protein interaction analyses [161,162]. Integration of GWAS with such data could thus facilitate a systems-based understanding of the pathogenic mechanisms.

Conclusion

Advances in genomics technology have initiated a myriad of novel genetic discoveries, including many common variants contributing to the risk of complex disease. This has led to a deeper understanding of the underlying biology and pathogenesis of these diseases. The genetic landscape of type 2 diabetes susceptibility is as yet incomplete, so far only explaining a small proportion of the total heritability of diabetes. Many possibilities for dissecting the architecture of type 2 diabetes aetiology have emerged in the form of large-scale genetic studies, meta-analyses, and sequencing in families. It has already greatly contributed to our understanding of disease mechanisms by identifying pathways that could not be linked to diabetes by existing hypothetical models, even though many genetic findings are recent and have yet to make their contribution to our knowledge about diabetes pathogenesis. However, one must bear in mind that diabetes is probably a much more diverse disease than the current subdivision into type 1 diabetes and type 2 diabetes implies, and more precise division into subgroups may both facilitate the investigation of type 2 diabetes genetics and pave the way for more individualized treatment. A holistic systems biology approach will also be required to obtain a complete picture of how genetic variation leads to diabetes. The rapid development of technology during the past years holds promises that this will be possible in the not too distant future.

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13 Genetics of Obesity

I. Sadaf Farooqi
Wellcome-MRC Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK

Key points

- Although the rise in prevalence of obesity is strongly influenced by environmental and social factors, within a given environment there is considerable variation in body weight.
- Some people appear to be more susceptible to obesity and it is clear that genetic factors play a major role in influencing the variation in body mass index in the population.
- Twin and familial studies have indicated that the heritability of body weight is 40–70%.
- Several intermediate traits are heritable, including energy intake, satiety responsiveness, basal metabolic rate, energy expenditure in response to a fixed amount of exercise, and body fat distribution.
- Up to 20% of children with severe obesity have rare chromosomal abnormalities and/or highly penetrant genetic mutations that drive their obesity.
- There are at least 30 Mendelian disorders characterized by developmental delay, dysmorphic features, and/or organ-specific developmental abnormalities in addition to obesity.
- Body weight is regulated by hypothalamic neurons, which integrate signals from adipose tissue stores and meal-related signals from the gastrointestinal tract. Rare mutations in several of the molecules involved in this signalling pathway cause severe obesity in humans without developmental delay.
- Common variants involving over 150 loci have been associated with body mass index and/or obesity in the population in genome-wide association studies.
- As many common variants lie in non-coding regions, the mechanisms by which they influence body weight have been challenging to dissect.

Obesity is defined as an excess of body fat which adversely affects health, most commonly by causing type 2 diabetes and cardiovascular disease. In addition, obesity is a cause of non-alcoholic fatty liver disease and a major cause of certain cancers [1]. As the direct measurement of adipose tissue mass requires specialist equipment (dual energy X-ray absorptiometry) that is not widely available, body mass index (BMI; weight in kg/height in m^2) is commonly used as a surrogate marker of adiposity. Based on World Health Organization criteria, people with a BMI >30 kg/m^2 are considered to have obesity. There is increasing recognition that the risk of type 2 diabetes is seen at a lower BMI in people of different ethnicities.

The prevalence of obesity has increased substantially in the last 40 years such that at least 20–25% of people in many high-income countries have obesity. There is no doubt that the rise in prevalence is strongly influenced by environmental and social factors, in particular the easy access to palatable, energy-dense, and highly processed food and reduced levels of physical activity during work and leisure time associated with urbanization. Socioeconomic factors play an important role: the prevalence of obesity in children and adults is twice as high in areas of socioeconomic deprivation compared to more affluent areas. However, within a given environment, there is considerable variation in body weight. Some people appear to be more susceptible to obesity, whereas others can remain thin despite the obesogenic environment. It is now clear that genetic factors play a major role in influencing the variation in BMI in the population.

Evidence for the genetic contribution to obesity

Classically the genetic contribution to a trait or disorder is estimated by studying twins to calculate heritability, the proportion of phenotypic variation that can be explained by genetic variation. Studies in monozygotic versus dizygotic twins, in particular in twins who were separated at birth and were then raised separately, have indicated that the heritability of body weight is 40–70% [2–4]. Similar estimates emerged from studies of children in the 1980s, during the obesity epidemic [5]. Additional evidence was provided by longitudinal studies of adopted children who were found to have body weights that are comparable to their biological rather than adoptive parents [6,7]. Extensive studies in twins and families (e.g. the Quebec family study) have shown that several intermediate traits are heritable, including energy intake, satiety responsiveness (fullness after a fixed meal), basal metabolic rate, energy expenditure in response to a fixed amount of exercise, and body fat distribution [8–10]. Elegant studies by Bouchard et al. showed that genetic factors influence the physiological response to overeating [11]. In a carefully supervised study in which identical twins were provided with excess calories, members of a twin pair gained similar amounts of weight, whereas there was considerable variability in the amount of weight gained by different sets of twins. Similarly, when twins were provided with a diet that led to a

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negative energy balance, members of a twin pair lost similar amounts of weight [12].

Finding the genes that regulate body weight

Different approaches have been used to identify the genes that regulate weight. The first, and to date the clearest, evidence supporting the genetic contribution to obesity comes from the study of people with severe obesity that begins in early childhood. Several genetic obesity syndromes display Mendelian inheritance (sometimes with incomplete penetrance). Genetic testing for these conditions is now recommended as part of the clinical assessment of people with severe obesity that begins before the age of 5 years [13]. For clinical purposes, it is useful to categorize the genetic obesity syndromes as those with dysmorphism and/or developmental delay and those without these features.

Obesity with developmental delay

There are at least 30 Mendelian disorders characterized by developmental delay, dysmorphic features, and/or organ-specific developmental abnormalities in addition to obesity (pleiotropic syndromes). There are many more potential disorders where specific chromosomal deletions or duplications have been reported in people with obesity and other features, but where the causative gene has not been established.

Prader-Willi syndrome

Prader-Willi syndrome is an autosomal dominant disorder caused by sporadic or, less commonly, inherited deletions of an imprinted region on the paternal chromosome 15q11–q13 [14]. Classic clinical features include low birth weight (in common with other imprinting syndromes), hypotonia, and poor feeding due to reduced swallowing reflexes, resulting in failure to thrive. Hyperphagia in early childhood results in severe obesity. Other features include impaired learning and development, behavioural abnormalities, and hypogonadotropic hypogonadism. Growth hormone deficiency leads to reduced linear growth and altered body composition, features that are improved by growth hormone treatment, which is often commenced in early childhood [15, 16].

Small deletions of small nucleolar RNAs (HBII-85 snoRNAs) recapitulate the classic features of Prader-Willi syndrome [17, 18], suggesting that these non-coding RNAs play a causal role in the syndrome. Reduced expression of brain-derived neurotrophic factor (BDNF), its receptor TrkB, and oxytocin may play an important role in the neurodevelopmental phenotype seen in individuals with Prader-Willi syndrome [19]. Clinical trials of intranasal oxytocin are being conducted in young children with the syndrome [20].

Albright hereditary osteodystrophy

Albright hereditary osteodystrophy is an autosomal dominant disorder caused by heterozygous loss-of-function mutations in *GNAS*, the gene encoding $G\alpha_s$ (stimulatory G-protein alpha subunit), which mediates G-protein-coupled receptor (GPCR) signalling [21]. Imprinting at the *GNAS* locus results in selective silencing of the paternally inherited *GNAS* allele in some tissues. Mutations on the maternally inherited *GNAS* allele are usually associated with hyperphagia and childhood-onset obesity, which is sometimes associated with low basal metabolic rate. Other classic features include low birth weight, developmental delay, brachydactyly, subcutaneous ossifications, short stature (height below the third percentile), and in some cases hormone resistance syndromes. This clinical spectrum is most often seen in individuals with non-sense or frameshift mutations. A more variable clinical phenotype is seen in those with missense mutations [22]. As such, screening for mutations in *GNAS* should be part of the diagnostic assessment of children with severe obesity [23]. Obesity-associated missense mutations in *GNAS* impair signalling through the melanocortin 4 receptor (MC4R), findings suggesting that therapies that enhance or bypass melanocortin signalling may be effective in these individuals.

Ciliary disorders

Several disorders affect the function of cilia, causing obesity with renal, retinal, and other organ-specific abnormalities. Bardet-Biedl syndrome is characterized by obesity, developmental delay, syndactyly, brachydactyly, or polydactyly, retinal dystrophy, hypogonadism, and renal abnormalities [24] caused by biallelic mutations in at least 20 genes that affect the function of cilia [25]. There is some evidence that Bardet-Biedl syndrome proteins affect leptin signalling and the MC4R agonist setmelanotide has been trialled in these individuals with some success [26]. Alstrom syndrome is an autosomal recessive condition that affects the centrosome and cilia, resulting in severe visual difficulties from infancy, with photophobia, nystagmus, and loss of central vision due to a rod-cone retinal dystrophy [27]. These individuals can develop a dilated cardiomyopathy in infancy, hepatic and renal dysfunction, hypothyroidism, hypogonadism (males), short stature, and mild to moderate developmental delay. Severe insulin resistance due to impaired adipose tissue expandability [28] results in the early development of type 2 diabetes, for which treatment with glucagon-like peptide-1 (GLP-1) receptor agonists can be effective.

BDNF, TRKB, and SH2B1 deficiency

BDNF signals through tropomyosin-related kinase B (TrkB) to regulate the development, survival, and differentiation of hippocampal and hypothalamic neurons [29]. Heterozygous deletions and missense mutations in BDNF and TrkB (often *de novo*) cause severe hyperphagic obesity, developmental delay, and a spectrum of neurobehavioural abnormalities, which include hyperactivity, stereotyped behaviours, autistic traits, impaired short-term memory, fearlessness, and in some cases aggression [30]. Src-homology-2 (SH2) B-adaptor protein-1 (SH2B1) is an adaptor protein that modulates signalling by receptor tyrosine kinases including TrkB and cytokine receptors including the leptin receptor (LEPR) [31]. Chromosomal deletions on 16p11.2 which include *SH2B1* [32] and heterozygous mutations in the gene itself [33] are associated with hyperphagia, dominantly inherited severe early-onset obesity, and disproportionate insulin resistance. Male mutation carriers often have behavioural problems, including social isolation and aggressive behaviour from childhood [33, 34], phenotypes seen in mice with brain-specific deletion of *SH2B1* and restored when gene expression is normalized in the brain [35].

Obesity without developmental delay

Experimental studies in rodents first showed that body weight is regulated by hypothalamic neurons that integrate signals from adipose tissue stores, such as leptin with short-term, meal-related signals from the stomach and gastrointestinal tract (PYY, GLP-1,

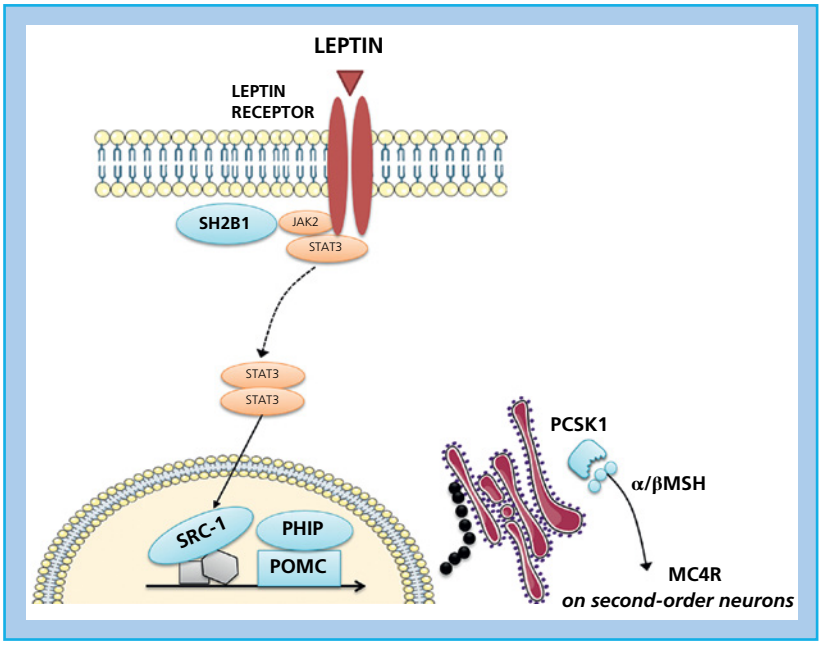

Figure 13.1 Molecular mechanisms involved in the maintenance of body weight in the hypothalamus. Leptin signalling in proopiomelanocortin (POMC) neurons. Leptin binds its receptor, which is expressed on the surface of the POMC neuron. This interaction leads to the phosphorylation of Janus kinase 2 (JAK2), which is potentiated by Src-homology-2 B-adaptor protein-1 (SH2B1). The next step is the phosphorylation of the transcription factor STAT3, which dimerizes and translocates into the nucleus. Here it interacts with steroid receptor coactivator (SRC)-1 to modulate the transcription of POMC. Pleckstrin homology domain–interacting protein (PHIP) interacts directly with DNA to regulate POMC transcription. POMC is cleaved to yield α- and β-MSH (melanocyte-stimulating hormone), which activate signalling by the melanocortin 4 receptor (MC4R). MC4R is expressed on second-order neurons, which receive projections from POMC neurons and act to decrease food intake. Mutations in these pathways can lead to severe obesity in humans.

CCK, and ghrelin) [36]. In the fed state, leptin stimulates the expression of proopiomelanocortin (POMC), which is cleaved by prohormone convertases to yield the melanocortin peptides, which act to reduce food intake through the MC4R. Mutations in several of these molecules cause severe obesity in humans (Figure 13.1).

Leptin and leptin receptor deficiency

Homozygous and compound heterozygous (different mutations on both alleles) loss-of-function mutations in the genes encoding leptin (*LEP*) and the leptin receptor cause rapid weight gain in infancy, resulting in severe obesity in the first year of life [37,38]. Children have an intense drive to eat (hyperphagia) [39,40]. Resting metabolic rate and total energy expenditure are appropriate for the degree of adiposity; impaired sympathetic nerve function likely contributes to impaired fat oxidation [41,42]. Both conditions are associated with hypothalamic hypothyroidism and delayed puberty due to hypogonadotropic hypogonadism. There is some evidence for delayed but spontaneous onset of menses [43]. Children have impaired T-cell function, consistent with high rates of childhood infection and a high rate of childhood mortality [41,42].

Congenital leptin deficiency can be diagnosed based on undetectable serum leptin concentrations. However, a small number of missense mutations that result in detectable but bioinactive circulating leptin have been reported [44]. While serum leptin levels are appropriate for the degree of obesity in most individuals with leptin receptor deficiency, specific mutations, which result in a truncated extracellular domain that binds leptin, can result in markedly elevated leptin levels [45]. Treatment of congenital leptin deficiency with recombinant leptin results in a dramatic improvement in hyperphagia, weight loss, and correction of thyroid and T-cell dysfunction (Figure 13.2) [39,42]. Leptin treatment permits the progression of appropriately timed pubertal development, suggesting that leptin is a permissive factor for the development of puberty [42]. Until recently, leptin receptor deficiency was not treatable. However, the MC4R agonist setmelanotide reduces hunger and weight loss in clinical trials [46] and is now licensed for the treatment of leptin receptor deficiency in many countries [47].

POMC and PCSK1 deficiency

Leptin stimulates the expression of the POMC precursor peptide, which is post-translationally processed into the melanocortin peptides α- and β-MSH (melanocyte-stimulating hormone). In the pituitary gland, POMC is cleaved to yield adrenocorticotrophin (ACTH), which acts on the melanocortin 2 receptor (MC2R) to regulate the synthesis of cortisol by the adrenal gland. In the skin, POMC-derived melanocortin peptides regulate pigmentation by signalling through the melanocortin 1 receptor (MC1R), and in the brain α- and β-MSH activate signalling via MC4R to reduce food intake [48]. As a result, homozygous or compound heterozygous mutations in POMC lead to hyperphagia and early-onset obesity, isolated ACTH deficiency (often presenting with neonatal hypoglycaemia or cholestatic jaundice), and hypopigmentation resulting in red hair in people of European ancestry [49,50].

Homozygous or compound heterozygous mutations in prohormone convertase 1 (PCSK1), the enzyme that processes POMC and other peptides, lead to hyperphagic severe early-onset obesity and ACTH deficiency as well as hypogonadotropic hypogonadism and postprandial hypoglycaemia due to impaired processing of proinsulin to insulin [51]. Where these assays are available, the finding of high proinsulin levels in the context of a low plasma insulin suggests this diagnosis. Impaired processing of gut-derived peptides in the enteroendocrine cells that express PCSK1 [52] may contribute to neonatal enteropathy; indeed, these individuals may first present to gastroenterologists with these symptoms. A single family with a homozygous mutation in carboxypeptidase E has been reported with overlapping clinical features [53]. Setmelanotide is effective in POMC and PCSK1 deficiency [54] and has been licensed for chronic weight management in these disorders.

MC4R deficiency

Targeted disruption of *Mc4r* in mice leads to increased food intake, weight gain, increased lean mass, and greater linear growth [55]. Heterozygous loss-of-function mutations in MC4R are found in 5–6% of individuals with severe early-onset obesity [56] and at a frequency of approximately 1 in 330 in the general UK population,

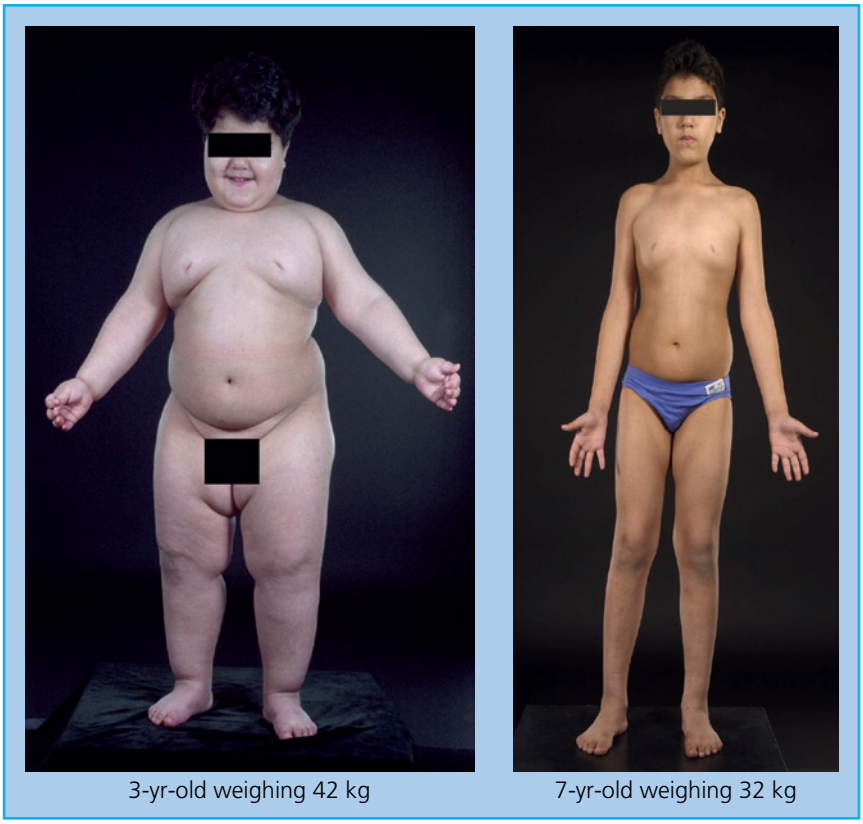

Figure 13.2 Recombinant leptin therapy reduces body weight in a child with congenital leptin deficiency.

making this the commonest gene in which variants contribute to obesity [57]. On average, at the age of 18 years, people who carry a heterozygous loss-of-function mutation in MC4R are ~18 kg heavier [57]. Most disease-causing MC4R mutations disrupt the expression and trafficking of the receptor to the cell surface [58]. Additionally, mutations can affect the production of cyclic adenosine monophosphate (cAMP), the homodimerization of MC4R, its endocytosis, as well as the recruitment of β-arrestins [59]. MC4R mutations are inherited in a co-dominant manner, with variable penetrance and expression in heterozygous carriers [56]; homozygous and compound heterozygous mutations have also been reported in people with severe obesity. The clinical features of MC4R deficiency include hyperphagia, early hyperinsulinaemia, increased lean mass, and increased linear growth [56, 60]. Complete loss-of-function mutations have a larger impact on phenotype than partial loss-of-function mutations [61].

Loss-of-function MC4R mutations in people are associated with a reduced prevalence of hypertension, relatively low systolic blood pressure, lower urinary noradrenaline excretion, and reduced peripheral nerve sympathetic activation compared to similarly obese people without MC4R mutations [62]. Liraglutide, the GLP-1 receptor agonist, is effective in some people with MC4R deficiency [63] and some individuals with heterozygous (but not homozygous) mutations benefit from Roux-en-Y bypass surgery [64].

SIM1 deficiency

SIM1 directs the development and function of the paraventricular nucleus of the hypothalamus where MC4R is highly expressed. Deletions that encompass SIM1 and heterozygous loss of function *SIM1* mutations cause hyperphagia, severe obesity, and increased linear growth, features that closely overlap with MC4R deficiency [65, 66]. Many SIM1 mutation carriers have speech and language delay in childhood and exhibit neurobehavioural abnormalities, including autistic-type behaviours. A small number of mutations in *OTP*, another transcription factor involved in paraventricular nucleus development, have been reported in individuals with obesity and autistic behaviours [67].

Rare variants in multiple genes associated with obesity

Alongside genetic disorders that follow a clear Mendelian pattern of inheritance, rare variants in several genes can drive obesity without always being causative in every variant carrier in the family. The characterization of these rare obesity-associated variants presents some challenges, but can be relevant for diagnostic and therapeutic purposes. Heterozygous loss-of-function mutations in POMC, which impair the function of α- and β-MSH, significantly increase obesity risk but are not invariably associated with obesity [68, 69]. Similarly, rare variants that impair the function of semaphorin 3 ligands, receptors, and co-receptors, which direct the development of melanocortin circuits, are associated with severe obesity [70]. Rare heterozygous variants that disrupt the function of the transcription factor steroid receptor coactivator (SRC)-1, which interacts with phosphorylated STAT3 to modulate leptin-mediated POMC transcription, are also associated with obesity [71]. Heterozygous pleckstrin homology domain–interacting protein (PHIP) deletions and frameshift mutations impair POMC transcription [72] and are associated with a variable spectrum of

developmental delay, reduced growth, hyperphagia, obesity, insulin resistance, and early type 2 diabetes. Informed by these mechanistic studies, clinical trials are ongoing to investigate whether setmelanotide may be effective in individuals with rare disorders affecting the melanocortin pathway.

Heterozygous mutations in the kinase domain of kinase suppressor of Ras2 (KSR2) are associated with reduced basal metabolic rate as well as hyperphagia in childhood [73]. Some KSR2 mutation carriers experience marked weight loss in childhood when prescribed the anti-diabetes drug metformin (for severe insulin resistance).

Conclusion

Cumulatively, up to 20% of children with severe obesity have rare chromosomal abnormalities and/or highly penetrant genetic mutations that drive their obesity [72]. This figure is likely to increase with greater detection driven by wider access to comparative genomic hybridization and whole-exome/genome sequencing. A genetic diagnosis can inform clinical management, as these individuals are relatively refractory to weight loss through changes in diet and exercise and several therapies now exist. A genetic diagnosis can inform decision making around bariatric surgery, which is feasible in some disorders (heterozygous MC4R deficiency), but high risk in others (homozygous leptin receptor deficiency and Prader-Willi syndrome) where the procedure does not address the underlying cause of the obesity.

Genetic studies continue to play a powerful role in shaping our understanding of the pathways regulating weight and their disruption in obesity and can inform strategies to target these pathways for the development of new weight loss strategies. Common variants involving over 150 loci have been associated with BMI and/or obesity in the population in genome-wide association studies (GWAS) [74]. Generally, each common variant has a very small effect size. For example, homozygous carriers of a common variant at the *FTO* locus, which has the greatest effect size seen in GWAS, are 2–3 kg heavier than non-carriers [75]. As many common variants lie in non-coding regions, the mechanisms by which they influence body weight have been challenging to dissect, but progress is being made [74]. There is increasing interest in the understanding of whether polygenic risk scores, which capture the cumulative effects of millions of common and rare variants combined and may predict the development of obesity [76], will be useful in clinical practice.

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14 Autoimmune Type 1 Diabetes

Omar Akel and Åke Lernmark
Department of Clinical Sciences, Lund University CRC, Skåne University Hospital, Malmö, Sweden

Key points

- The prevalence and incidence of autoimmune type 1 diabetes continue to increase worldwide.
- The clinical onset peaks in childhood, but may occur across the age span.
- Autoimmune type 1 diabetes aetiology is marked by the appearance of a first β-cell autoantibody against either insulin or glutamic acid decarboxylase 65 (GAD65). Some children may present with both autoantibodies.
- The natural history of type 1 diabetes may be divided into three distinct stages:
  - The development of multiple β-cell autoimmunity: Stage 1.
  - Asymptomatic loss of β-cell secretory capacity: Stage 2.
  - Loss of β-cell function along with diabetes symptoms: Stage 3.
- Autoimmune type 1 diabetes results from a loss of immunological tolerance to certain β-cell autoantigens.
- Human leucocyte antigen (HLA) genes represent the strongest genetic determinants for the risk of β-cell autoimmunity, but may not contribute to the progression to type 1 diabetes.
- Environmental factors may trigger β-cell autoimmunity, accelerate the pathogenic process, or both.
- β-cell destruction occurs during the pathogenesis of β-cell autoimmunity and is likely to be mediated by cytotoxic CD8+ T cells.
- β-cell destruction may occur prior to β-cell autoimmunity, but the precise mechanism remains unclear.
- Multiple β-cell autoantibodies (≥2) usually appear within 6–12 months following the appearance of the first autoantibody and markedly increase the risk for progression to type 1 diabetes.
- The appearance of either autoantibodies against islet antigen-2 (IA-2) or zinc transporter 8 (ZnT8) in children with insulin or GAD autoantibodies is a strong marker of accelerated progression to the clinical onset of type 1 diabetes.
- The progressive destruction of β cells is likely to vary in intensity and duration, affecting the time between the first appearance of the autoantibody biomarker and the clinical diagnosis.

The differentiation between type 1 diabetes (previously known as insulin-dependent diabetes or juvenile-onset diabetes) and type 2 diabetes (non-insulin-dependent or adult-onset diabetes), the two main forms of diabetes, has been deliberated for almost 60 years. Insulitis was rediscovered in 1965, supporting the view that islet mononuclear cell infiltration was associated with the development of type 1 diabetes [1]. The evidence for islet autoimmunity was further supported by the identification of mononuclear cell reactivity with islet extracts [2] and the association between type 1 diabetes and other organ-specific autoimmune disorders [3]. More importantly, long sought-after autoantibodies against islet cells (ICAs) were reported using indirect immunofluorescence on pancreas frozen sections and sera of people with concomitant type 1 diabetes and autoimmune polyendocrine syndrome [4, 5]. At the same time, type 1 diabetes was found to be strongly associated with human leucocyte antigen (HLA) [6, 7]. It was also noted, however, that ~10% of adults diagnosed with type 2 diabetes whose sulfonylurea treatment had failed (so-called *secondary failures*) [8] were positive for ICAs, a group of people now commonly known as having latent autoimmune diabetes of adults [9–11]. There are several genetic and autoimmune similarities between childhood and adolescent type 1 diabetes and latent autoimmune diabetes of adults, but the two entities differ in genetic and autoimmune processes as well as the clinical features [11, 12]. Several years of research, initiated by studying children from birth followed by genetic studies [13–18], have resulted in a paradigm shift of the understanding of the aetiology and pathogenesis of type 1 diabetes. In this chapter, we summarize the current knowledge of possible trigger(s) of β-cell autoimmunity (aetiology) and factors affecting the progression to the clinical onset in individuals who have developed one or more β-cell autoantibodies (pathogenesis).

ICAs were described in 1974 [4, 5], islet surface antibodies (ICSAs) in 1978 [19], and complement-dependent antibody-mediated islet cell cytotoxicity in 1980 [20]. The first autoantigen recognized by islet antibodies, an islet protein of 64 000 relative molecular mass (64 K), was described in 1982 [21]. The 64 K protein had glutamic acid decarboxylase (GAD) activity [22], but molecular cloning showed that the human islet GAD was a novel isoform, GAD65 [23]. Autoantibodies to insulin were demonstrated in 1983 [24]; to islet antigen-2 (IA-2), a tyrosine phosphatase-like protein, in 1994 [25]; and to the zinc transporter 8 (ZnT8) in 2007 [26]. In contrast to T-cell analyses, GAD65, IA-2, and ZnT8 autoantibodies may be determined in standardized assays [27].

Autoimmune type 1 diabetes is recognized by the appearance of a first β-cell autoantibody against either insulin (IAA) or GAD65 (GADA), or both, in early childhood [28–30]. Rarely, the first islet

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Table 14.1 Biomarkers of islet autoimmunity predict clinical onset of type 1 diabetes.

Autoantibody abbreviation	Protein autoantigen	Protein abbreviation	Gene and location	References
IAA	(Pro)insulin	Insulin	*INS* 11p15.5	[24,33]
GADA	Glutamic acid decarboxylase	GAD65	*GAD2* 10p12.1	[21–23,34]
IA-2A	Islet antigen-2	IA-2	*PTPRN* 2q35	[25,35,36]
ZnT8A	Zinc transporter 8	ZnT8	*SLC30A8* 8q24.11	[26,37,38]

autoantibody is directed against IA-2 (IA-2A) or ZnT8 (ZnT8A) [28,30–32]. These four autoantibodies (Table 14.1) are strong biomarkers, since the development of a first autoantibody (IAA or GADA) and the appearance of a second, a third, and often a fourth autoantibody will result in type 1 diabetes in 100% of individuals when followed for 10–20 years [18,32,39]. The epidemiology of β-cell autoantibodies in children or adults in different countries is currently unknown, as population screening for IAA, GADA, IA-2A, and ZnT8A is yet to be implemented. It remains to be determined in multiple populations whether the incidence of β-cell autoantibodies eventually equals that of type 1 diabetes.

Epidemiology

The incidence of type 1 diabetes varies 50–100-fold worldwide, with the highest rates occurring in individuals of northern European descent (Figure 14.1). In most countries, the lifetime risk of type 1 diabetes is less than 1%. Both sexes are equally affected in childhood, but men are affected more commonly in early adult life [41,42]. An incidence rate of 20 per 100 000 individuals per year corresponds approximately to a cumulative incidence of 0.3% at age 15 years, or 1 in 330, and a prevalence in age group 0–15 years of ~0.15%. The incidence of childhood type 1 diabetes is rising rapidly in all populations, especially in children younger than 5 years, where the incidence in Europe has doubled during the last 20 years [42]. The 2–4% increase per year would correspond to doubling times of 35–18 years. Because of the wide differences in absolute incidence rates across countries (Figure 14.1), the magnitude of change over time appears somewhat suppressed in the low-incidence regions such as Japan. There is a tendency that low-incidence countries have experienced a larger relative increase than high-incidence countries. The increasing incidence of type 1 diabetes suggests a major environmental contribution. However, given the significant decrease in incidence rate among children reported in Australia [43] and Finland [44], the role of specific pathogenic factors remains largely unsettled; nevertheless, recent longitudinal observational clinical studies of children at increased genetic risk for type 1 diabetes are providing novel insights into possible mechanisms of virus infections [45,46].

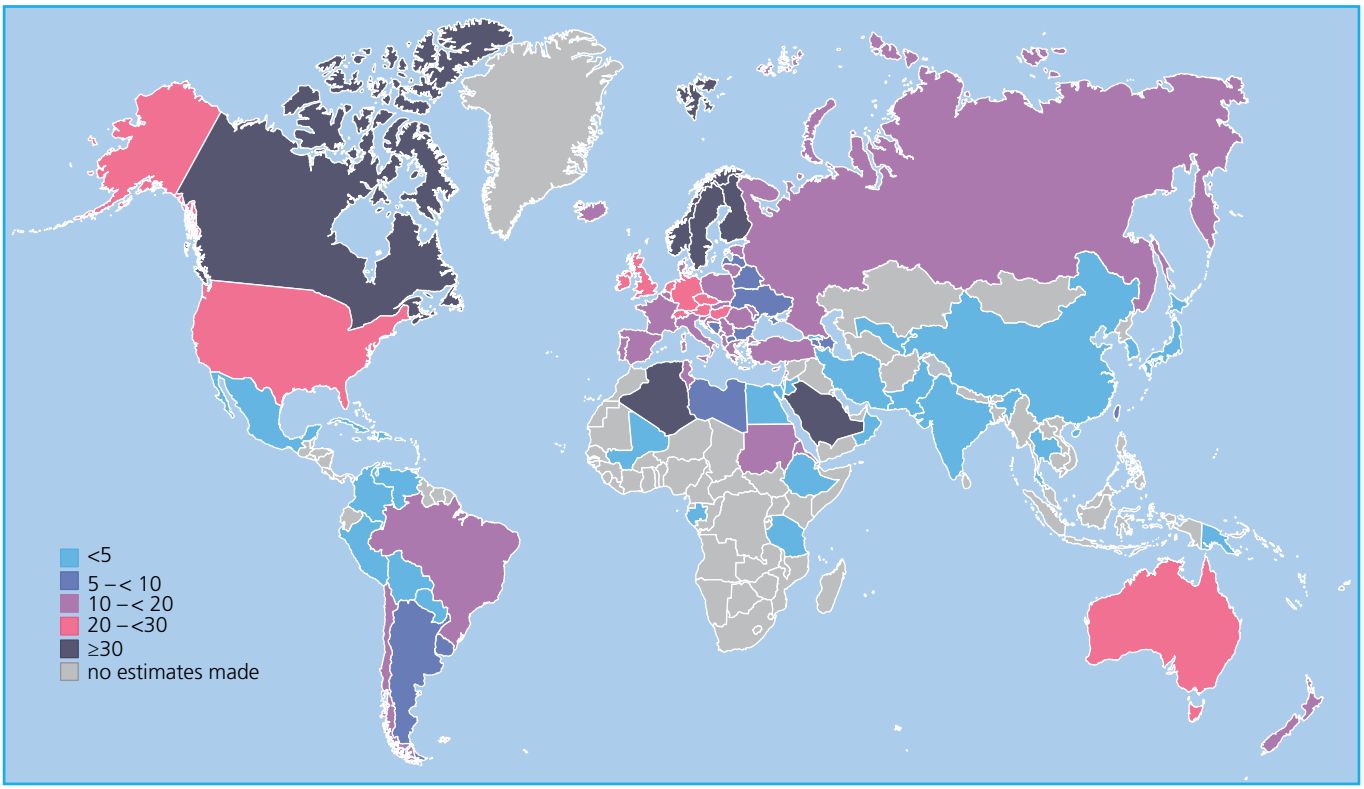

Figure 14.1 Age–sex standardized incidence rates (per 1 000 000 population per year) of type 1 diabetes in those 0–14 years of age. Source: Adapted from Sun H et al. 2022 [40].

The incidence rates of type 1 diabetes are from the time of clinical onset, but the incidence rate of islet autoimmunity is largely unknown and islet autoimmunity may have been present for several years. The clinical onset represents the end-point of a progressive, silent pathogenesis. The rate of loss of pancreatic β cells is difficult to estimate and may be affected by environmental factors. For example, enterovirus infection in children who are positive for two or more islet autoantibodies may accelerate the pathogenesis and result in an earlier age at onset [47].

The epidemiology of type 1 diabetes represents two stages. The first stage reflects the aetiology, the actual trigger of the disease that includes the genetic and environmental aetiology. Currently, the genetic aetiology indicates that the HLA haplotypes DR4-DQ8, DR3-DQ2, or both (the genotype is DR3-DQ2/DR4-DQ8) are necessary but not sufficient for the disease [48]. The environmental aetiology may represent enterovirus infection and prolonged viral shedding and possibly other factors (genetic as well as environmental) [45,46,49,50] in combination that trigger islet autoimmunity reflected by the appearance of a first islet autoantibody. Dependent on the HLA type and other genetic factors of the child, the first appearing autoantibody may be either IAA or GADA [28,30,51–53]. Future studies of the epidemiology of autoimmune type 1 diabetes should therefore take into account not only the clinical onset of the disease, referred to as *type 1 diabetes* or *autoimmune diabetes*, but also the epidemiology of *islet autoimmunity* or *autoimmune islet disease* [54]. At present, autoimmune islet disease is defined by the presence of persistent islet autoantibodies, IAA, GADA, IA-2A, and ZnT8A, in various combinations.

The epidemiology of autoimmune islet disease would be important to better understand the relationship to infections, but also genetic propensity and contributions by other environmental factors. A program of primary care–based screening showed an islet autoantibody prevalence of 0.31% among children aged 2–5 years in Bavaria, Germany [55]. Testing islet autoantibodies at random or in select populations such as schoolchildren should inform about the epidemiology of autoimmune islet disease and what to expect in the years to come about the epidemiology of autoimmune type 1 diabetes.

Natural history and staging type 1 diabetes

The description of the natural history of autoimmune type 1 diabetes has changed in a major way during recent years. The aetiology and pathogenesis are better understood, especially as the aetiology can be better defined in terms of genetic and environmental aetiology and that the cause and origin of autoimmune type 1 diabetes are beginning to be understood. First, HLA genetic risk for type 1 diabetes allowed screening to identify neonates at increased genetic risk [15,56]. Second, islet autoantibodies detected in standard radiobinding assays were validated and found to be reliable biomarker end-points of islet autoimmunity [57–60]. The four commonly used islet autoantibody markers (Table 14.1) are detectable not only in radiobinding assays but also in double-sided enzyme-linked immunosorbent assay (ELISA) [61], chemiluminescence [62,63], and autoantibody detection by agglutination polymerase chain reaction (ADAP) [64]. Third, general population screening at birth has been proven to be both feasible and well tolerated by parents and children [65–68].

Follow-up studies from birth in more than 26 000 individuals in nine different studies have made it possible to stage the pathogenesis of type 1 diabetes (Figure 14.2). The Environmental Determinants of Diabetes in the Young (TEDDY) study is by far the largest and represents a major effort by the National Institutes of Health (NIH) that brought DIPP, DAISY, DiPiS, BABYDIAB, PANDA, and DEW-IT (Table 14.2) together to increase the power of the

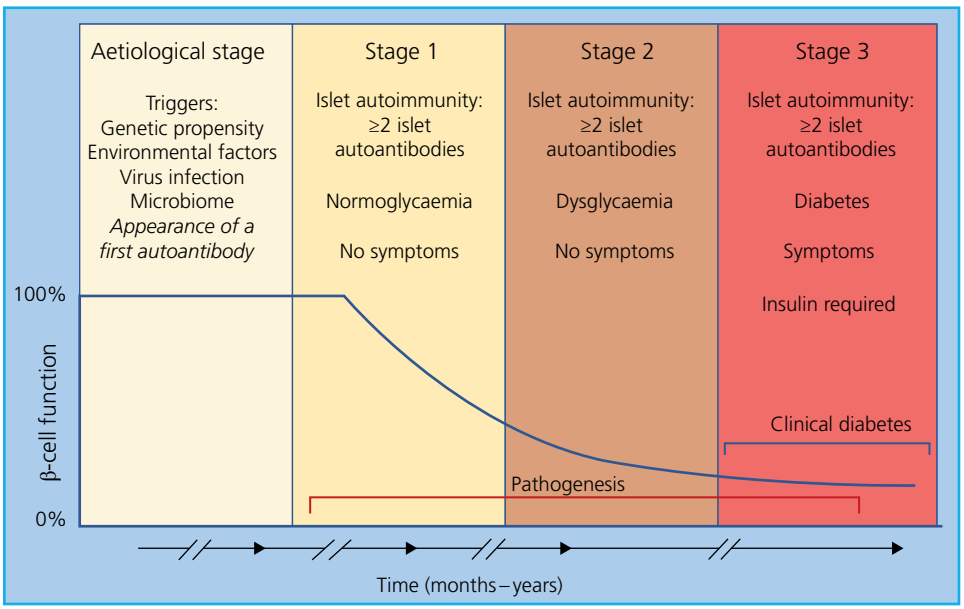

Figure 14.2 Staging of the natural history of autoimmune type 1 diabetes. The aetiological stage is thought to be associated with enterovirus infection in people at increased genetic risk for type 1 diabetes. A series of unknown events, such as prolonged shedding of virus, may trigger islet autoimmunity by yet unknown mechanisms. A first islet autoantibody against islet antigen or glutamic acid decarboxylase, dependent on genetic risk, appears and represents the biomarker for islet autoimmunity. Following the appearance of a second autoantibody, the person is classified in stage 1, which is defined by the presence of two or more islet autoantibodies, normoglycaemia, and no symptoms. In stage 2 the person has multiple autoantibodies and has developed dysglycaemia or impaired glucose tolerance without symptoms. Stage 3 is also characterized by multiple autoantibodies. Individuals may lose autoantibodies prior to stage 3. Diabetes is diagnosed according to the American Diabetes Association and World Health Organization criteria and the person may have symptoms and will also require insulin. Sources: Adapted from Insel et al. 2015 [82] and Lloyd et al. 2022 [116].

Table 14.2 Observational birth cohorts in autoimmune type 1 diabetes.

Year start	End	Acronym	Name	Newborns followed	Inclusion	Reference
1994	Ongoing	BABYDIAB	Baby Diabetes	1610	FDR	[13]
1994	Ongoing	DAISY	Diabetes Autoimmunity Study in the Young	1339	FDR and HLA	[16, 69]
1994	Ongoing	DIPP	Diabetes Prediction and Prevention	3720	HLA	[14, 15]
2000	2019	DiPiS	Diabetes Prediction in Skåne	6831	HLA	[70–72]
2000	2004	PANDA	Prospective Assessment of Newborn for Diabetes Autoimmunity	453	HLA	[73]
2001	2004	DEW-IT	Diabetes Evaluation in Washington	1000	HLA	[74]
2004	Ongoing	TEDDY	The Environmental Determinants of Diabetes in the Young	8676	HLA	[17, 75]
1997	Ongoing	ABIS	All Babies in South East Sweden	17 055	Population	[76, 77]
2001	Ongoing	MIDIA	Environmental Triggers of Type 1 Diabetes	908	HLA	[78, 79]
2012	Ongoing	ENDIA	Environmental Determinants of Islet Autoimmunity	1473	FDR	[80, 81]

FDR, first-degree relative; HLA, human leucocyte antigen.

investigation. Because type 1 diabetes is detected in most individuals with type 1 diabetes after a relatively short period of symptoms, the natural history of the disease has been poorly defined until recently. With the current ability to define individuals at increased risk for type 1 diabetes based on high-risk HLA and islet autoantibodies, the understanding of the pre-diabetes period is improving.

The prospective studies from birth of children with increased risk for type 1 diabetes in TEDDY and the other studies listed in Table 14.2 have revealed that GADA, IAA, IA-2A, or ZnT8A may develop several years before the clinical diagnosis. The sequence of events preceding the diagnosis of overt type 1 diabetes would include the following:

1. Genetic predisposition.
2. Overt immunological abnormality, reflected in a first-appearing islet autoantibody but with normal glucose levels and no symptoms.
3. Development of a second or third islet autoantibody, still with normal blood glucose and no symptoms (type 1 diabetes stage 1).
4. Development of β-cell dysfunction and dysglycaemia, but no symptoms (type 1 diabetes stage 2).
5. Development of overt hyperglycaemia with detectable C-peptide (type 1 diabetes stage 3).
6. The final stage of insulin dependency, with loss of detectable C-peptide (Figure 14.2) [82].

The fact that type 1 diabetes develops in people of all ages must be considered when studying the natural history in children and adults. Early histological studies of pancreatic tissue of people who died shortly after the clinical onset of diabetes revealed that the pancreatic islets were altered by fibrosis, hyalinosis, atrophy, and infiltration of inflammatory cells [1]. The inflammatory lesion of the islets of Langerhans was described as *insulitis*, and quantitative studies of the pancreatic islets showed a specific loss of insulin-positive cells in association with the clinical onset of type 1 diabetes [1]. It was therefore suggested that the pathogenesis of type 1 diabetes involved autoimmune reactions directed towards the endocrine pancreas. This notion was supported by leucocyte migration inhibition to pancreatic islet antigens [2]. Numerous studies have confirmed the presence of insulitis [83–85], however, despite the assumption that type 1 diabetes is a T-cell mediated disease, reproducible and standardised tests of blood T-cell reactivity against islet autoantigens or other specific autoantigens are yet to be fully established.

Islet autoantibodies as biomarkers

Islet autoantibodies have been studied longitudinally in a large number of first-degree relatives of people with type 1 diabetes until the clinical onset of type 1 diabetes [86–88]. The islet autoantibodies are not thought to be directly involved in β-cell destruction. For example, complement-mediated antibody-dependent cytotoxicity would require the autoantigen to be expressed on the β-cell surface [19, 20]. A subset of autoantibodies to ZnT8 may fulfil the criteria for cell surface expression [89, 90]. Further studies are needed to fully establish to what extent islet autoantibodies *per se* contribute to pathogenesis and risk for diabetes. The demonstration of islet autoantibodies years before the onset of clinical symptoms has made it possible to identify individuals at high risk for type 1 diabetes and to initiate therapeutic intervention trials. In particular, the number of islet autoantibodies seems to affect the rate of progression to clinical onset [39]. Children recruited and followed in three studies (DAISY, Colorado, n = 1962; DIPP, Finland, n = 8597; and BABYDIAB, Germany, n = 2818) were merged in a joint analysis [39]. The data showed that progression to diabetes at 10-year follow-up after islet autoantibody seroconversion varied with the number of islet autoantibodies: no islet autoantibodies was 0.4% (95% confidence interval [CI], 0.2–0.6%); a single islet autoantibody was 14.5% (95% CI, 10.3–18.7%); and multiple islet autoantibodies was 69.7% (95% CI, 65.1–74.3%) [39]. These results were further corroborated in 1815 first-degree relatives who were

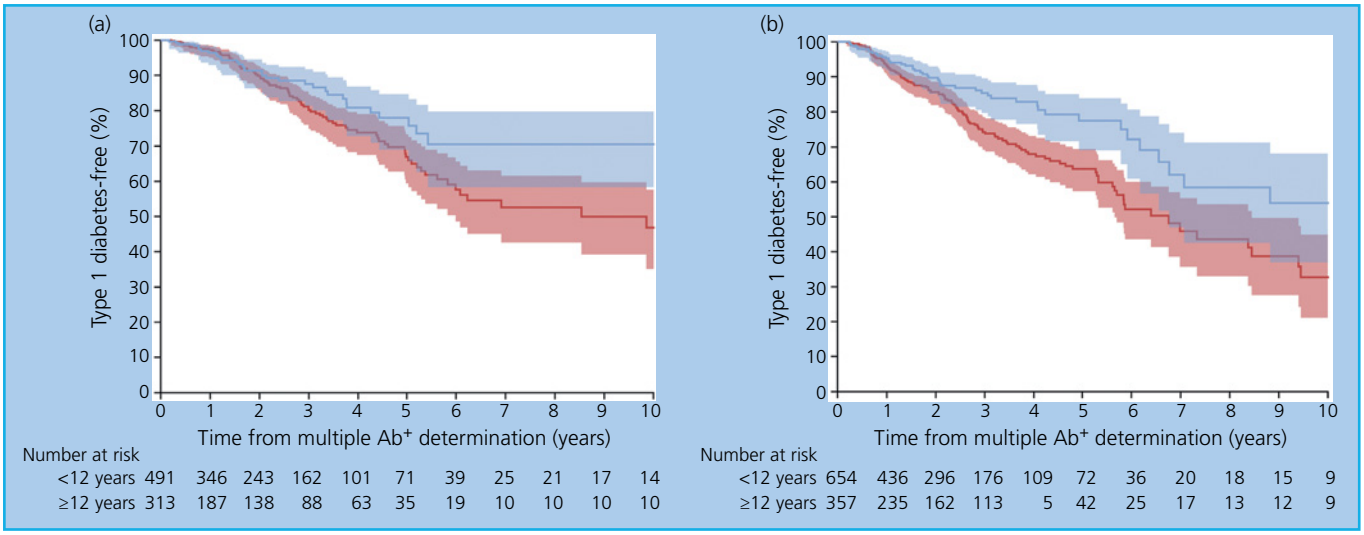

Figure 14.3 Type 1 diabetes-free cumulative incidence with 95% confidence interval (shaded area) in TrialNet participants with two (a) or more than two (b) islet autoantibodies. (a) In participants with two autoantibodies, there was a lower cumulative incidence among those older than 12 years of age (blue) compared to those younger than 12 years of age (red) ($p = 0.0496$). (b) In participants with more than two autoantibodies, the cumulative incidence was markedly different between those younger than 12 years (red) and those older than 12 years of age (blue) ($p = 0.0008$). Source: Jacobsen et al. 2020 [91].

followed until diabetes diagnosis in the TrialNet Pathway to Prevention study (Figure 14.3) [91]. Participants younger than 12 years had a higher risk of progressing to clinical onset regardless of whether they had two autoantibodies only (panel a) or more than two autoantibodies (panel b) [91]. These data raise the question of whether islet autoantibody screening should be used in clinical practice. The effect of age and number of autoantibodies strongly suggests that the heterogeneity in progressing to clinical onset needs to be taken into account in secondary prevention clinical trials.

A first step was to use a meta-analysis to assess the evidence of an association between islet autoantibodies and the development of type 1 diabetes in a pooled population of both genetically at-risk individuals and people without a definite genetic background [92]. In the meta-analysis, 21 prospective cohort studies with 71 482 participants, who were followed for a median of 7 years and of whom 926 developed type 1 diabetes, evaluated the role of islet autoantibodies in prediction of type 1 diabetes progression. Compared to people without autoantibodies, those positive for any type or number of islet autoantibody had a marked risk for type 1 diabetes (risk ratio [RR] 150.42 [95% CI 87.34, 259.04]) [92]. People with multiple autoantibodies had a ninefold higher risk than those with a single islet autoantibody. This meta-analysis is raising the question of the place of screening the general population for islet autoantibodies, since the likelihood of individuals with multiple islet autoantibodies eventually developing type 1 diabetes is high.

A second step was the recent discovery that the aetiology of islet autoimmunity may represent two different endotypes, dependent on whether IAA appear first compared to GADA [28, 30]. This raises the question of whether the first-appearing autoantibody is related to disease progression. In longitudinal sampling of IAA, GADA, and IA-2A in a cohort of 24 662 people combined from DAISY [16], DIPP [93], DiPiS [94], DEW-IT [75], and BABYDIAB [95], 2172 individuals fulfilled the criteria of two or more follow-up visits and autoantibody positivity at least once, while 652 progressed to type 1 diabetes during 15 years of follow-up (Figure 14.4). Continuous-time hidden Markov models [18] were used to let the data visualize the latent health state of the participants during 5 years of follow-up. Three different trajectories were discovered from 11 latent states. TR1 represents those with multiple islet autoantibodies in the first sample. Only 40% remained diabetes free after 5 years. TR2 represents people with predominantly IAA as the first-appearing autoantibody. Diabetes-free survival was 62%. TR3 was people with GADA first who showed 88% diabetes-free survival after 5 years of follow-up. Progression rates within each trajectory could be refined by age, sex, and HLA-DR, thereby providing a clinically useful prediction of disease onset [18]. This type of approach with the aid of further machine learning and artificial intelligence may provide the means by which islet autoantibody analyses will become meaningful for the individual.

Genetic and environmental aetiology to initiate islet autoimmunity

Genetic aetiology

Longitudinal studies of newborn children at increased genetic risk either as a first-degree relative (father, mother, or sibling has type 1 diabetes) or by cord blood HLA typing have identified infants who developed a first islet autoantibody during the first year of life [13, 28, 30]. The first autoantibody was either IAA or GADA, rarely IA-2A or ZnT8A, but two or more autoantibodies occurred as blood sampling was not more frequent than three months apart. There was a strong association between HLA-DR4-DQ8 and IAA as the first β-cell autoantibody [28, 31]. GADA as a first islet autoantibody was associated with HLA-DR3-DQ2; indeed GADA-first was exclusive to homozygous HLA-DR3-DQ2 children [28, 31]. These observations suggest a paradigm shift in the understanding of the association between HLA and type 1 diabetes. The primary effect would be an association between HLA and the first-appearing autoantibody and not type 1 diabetes *per se*. The mechanism by which HLA contributes to the aetiological triggering of islet autoimmunity should be sought, as it may have nothing to do with loss of β cells, dysglycaemia, and diabetes [53, 96].

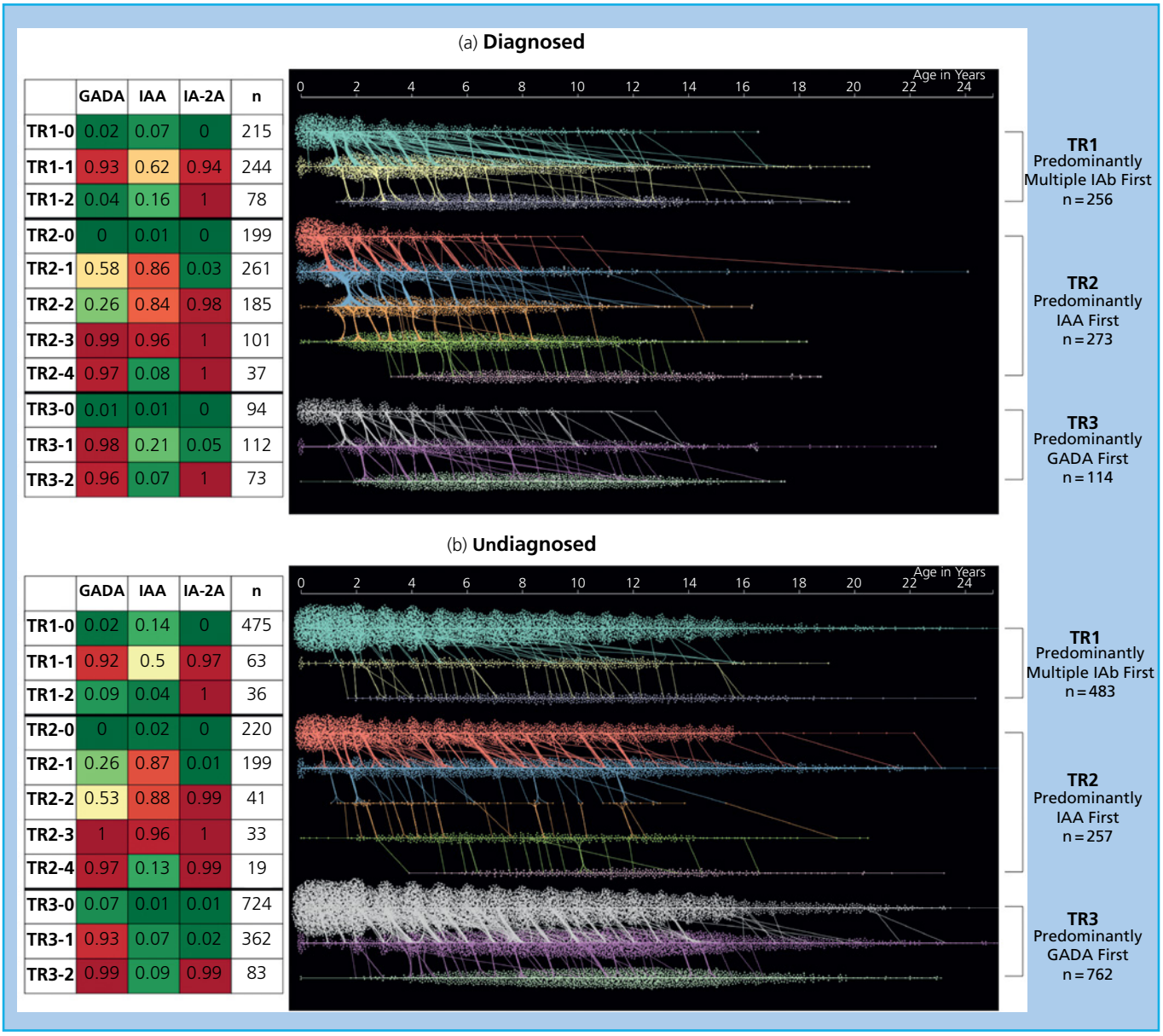

Figure 14.4 Three trajectories of data-driven islet autoantibodies towards stage 3 diabetes. A 11-state hidden Markov mode discovered the three trajectories for (a) diagnosed (D, 643 individuals who were diagnosed with type 1 diabetes) and (b) undiagnosed (UD, 1502 individuals who remained not diagnosed with diabetes during follow-up). The data in the table to the left describe the 11 states as the probabilities for each islet autoantibody (glutamic acid decarboxylase autoantibody [GADA], insulin autoantibody [IAA], or islet antigen-2 autoantibody [IA-2A]) for each state (the heat map indicate green for 0 and red for 1). Waterfall diagrams to the right show visits (dots) and the respective trajectory state over time in years (x-axis). Each person is depicted from the appearance of the first autoantibody and can then be followed from one state to the next in the waterfall. The three trajectories reveal themselves as TR1, predominantly multiple islet autoantibodies (IAb) as the first islet autoantibody (256 D, 483 UD); TR2, predominantly IAA first (273 D; 257 UD); and TR3, predominantly GADA first (11 D; 762 NP). P, progressors; NP, non-progressors. Source: Kwon et al. 2022 [18]. Licensed under CC BY 4.0.

The genetics of type 1 diabetes have been studied extensively during the past 50 years, especially since the mode of inheritance has remained uncertain. HLA represents ~50% of the familial risk of type 1 diabetes [97]. It should be noted that alleles in the HLA region, such as the HLA class II DR and DQ alleles, are in linkage disequilibrium, which means that among hundreds of alleles certain allele combinations are inherited as extended haplotypes. The reduced rate of recombination events in the HLA region is not understood and it complicates the dissection of which allele and protein product is mechanistically responsible for the association between HLA and the first-appearing islet autoantibody. A suitable example is the recently discovered tri-SNP (single-nucleotide polymorphism) in the first intron of HLA-DRA [98,99]. The HLA-DRA protein, representing the A-chain of the DR heterodimer, does not vary between people. However, the recent finding suggests the presence of an intron polymorphism that may regulate the expression not only of HLA-DR, but also the DQ heterodimer [98,99].

The class II HLA-DR-DQ haplogenotype DR3-DQ2 (*DRB1*03-DQA1*0501-B1*0201*)/DR4-DQ8 (*DRB1*04-DQA1*03:01-B1*03:02*) confers the highest risk for type 1 diabetes [48]. The risk of the heterozygous DQ2/8 genotype for type 1 diabetes is complicated by the possibility that *DQA1*05:01-B1*03:02* and *DQA1*03:01-B1*02:01* haplotypes form heterodimer molecules in *trans* that contribute to risk by unique antigen-presenting capabilities [100]. The

HLA DQ2/8 genotype may therefore represent not only two but four potential antigen-presenting heterodimers. The DR3-DQ2/DR4-DQ8 genotype was found in more than 95% of individuals with type 1 diabetes younger than 30 years of age compared to 25–30% of the general population [101]. The HLA DR3-DQ2 and DR4-DQ8 haplotypes, alone or in combination, may therefore be regarded as necessary but not sufficient for aetiology currently measured as the risk of developing a first-appearing islet autoantibody (Figure 14.2). In children developing a second islet autoantibody, the risk that the pathogenesis will end up in clinical onset has been estimated as 70% within 10 years [32,39].

HLA DR-DQ genes are transcribed and translated into the α and β transmembrane chains that pair to form a heterodimer (Figure 14.5). The heterodimer creates a peptide-binding region between the α- and β-chains. The peptide-binding region has pockets to bind amino acid residues, but it is the physicochemical nature of the peptide-binding region that dictates the binding of peptides from exogenous and endogenous protein antigens (Figure 14.5). The peptide-binding region with bound peptide is the ligand, the trimolecular complex, for the T-cell receptor (TCR). The genetic aetiology of islet autoimmunity is reflected by the amino acid residues coded for by different DRB1* [102] and DQA1*-DQB1* for either risk [103, 104] or protection [104, 105]. Amino acid residues associated with islet autoimmunity were αa1, α44, α157, α196 on the DQ A-chain, and β9, β30, β57, β70, β135 on the DQ B-chain. These motifs capture all known susceptibility and resistant type 1 diabetes associations. Three motifs, DCAA-YSARD (representing DQ2.5), DQAA-YYARD (representing DQ8), and DQDA-YYARD (representing DQ8.1), accounted for the structures needed to develop islet

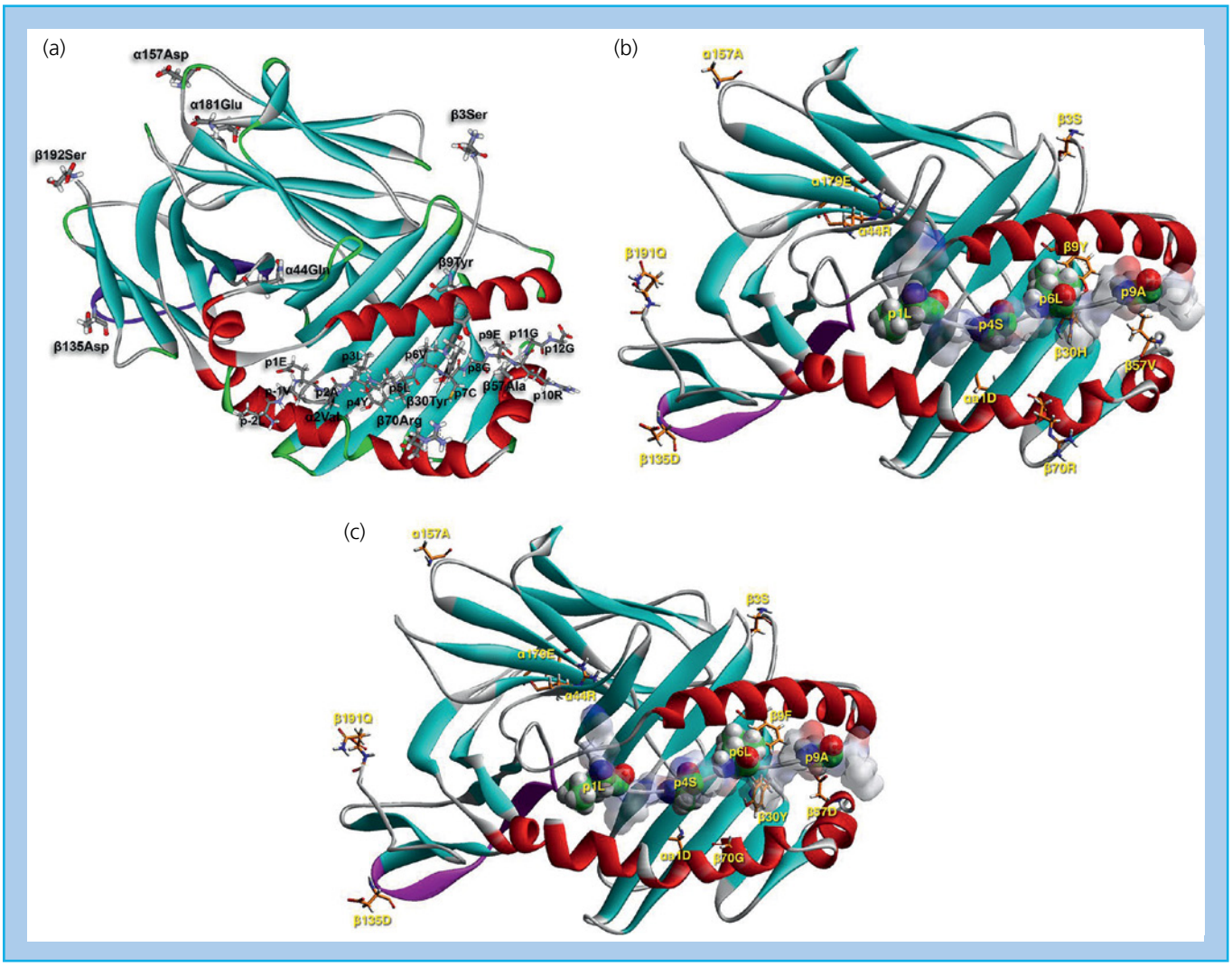

Figure 14.5 Molecular illustrations of insulin peptides bound to (a) human leucocyte antigen (HLA)-DQ heterodimers at risk (DQ8 with insulin B11–24); (b) neutral risk (DQ6.4 with insulin B5–15); and (c) protection (DQ6.2 with insulin B5–15). (a) is based on a crystallized complex while (b) and (c) are based on molecular simulations. The HLA-DQ-insulin peptide complexes are shown in their secondary structure formation (α-helix in red; β-sheet in turquoise; β-turn, random coil, or any other form in grey). The β134–148 CD4-binding stretch is shown in purple. The HLA-DQ amino residues in both the A- and B-chains are shown in stick form (atom colour convention: carbon, grey; oxygen, red; nitrogen, blue; sulfur, yellow; hydrogen, white). The insulin peptide is shown in stick form in (a) (thinner sticks, with the same colour convention), and in space-filling form in (b) and (c) with the p1Leu, p4Ala, p6Leu, and p9Ala anchor residues opaque. The remaining residues are non-transparent surfaces coloured by atom charge (red, negative; blue, positive; partial charges coloured with shades in between), in order to appreciate the positioning and orientation of the different amino acid residues. The trimolecular complexes depicted in (a–c) from risk to protection are clearly different in appearance to indicate that T-cell receptors on CD4+ T cells will differ markedly in binding characteristics to go from risk to protection.

autoimmunity and risk for type 1 diabetes. Ten motifs were significantly associated with resistance to type 1 diabetes [104]. The nine amino acid residues were within or near anchoring pockets of the peptide-binding region (α44, β9, β30, β57, and β70); one was the N-terminal of the alpha chain (αa1), one in the CD4-binding region (β135), one in the putative cognate TCR-induced αβ homodimerization process (α157), and one in the intra-membrane domain of the alpha chain (α196) (Figure 14.5). These motifs are critical to the understanding of the mechanisms by which immunological tolerance is broken and islet autoimmunity is allowed to develop. The structure and physicochemical property of the highest-risk HLA class II molecules have been specified and the question that remains to be answered is what peptides will form a trimolecular complex that interact with CD4+ T cells able to trigger islet autoimmunity.

The concomitant inheritance of both HLA and non-HLA high-risk alleles and haplotypes appears to increase the risk of type 1 diabetes significantly through synergistic association of their single risks. In individuals with type 1 diabetes, DQ8 (*DQA1*0301-B1*0302*) is mostly inherited with variants of *DRB1*04*, especially *DRB1*04:01*, *DRB1*04:04, DRB1*04:05* or *DRB1*04:02*, but not *DRB1*04:03* or *DRB1*04:07*. *DRB1*04:01* confers a higher risk than *DRB1*04:04*, while *DRB1*04:03* or *DRB1*04:07* is negatively associated with type 1 diabetes [106, 107]. The limited genetic differences between these alleles are reflected in the structure of the heterodimeric proteins formed by the DRA-coded A-chain and the DRB1-coded B-chain. The peptide-binding groove attains physicochemical characteristics that differ between the heterodimers despite a limited number of amino acid substitutions [102, 108]. These amino acid substitutions may account for most of the *DRB1*04* contribution to type 1 diabetes risk. Further studies are needed to establish the way genetic polymorphisms within the HLA region are related to the binding of peptides and subsequent antigen presentation that can be linked to the risk of developing a first autoantibody as a biomarker of the initiation of islet autoimmunity.

The most common protective haplotypes are DQ6 (*DQA1*01:02-B1*06:02* and *DQA1*01:02-B1*06:03*) and also *DQA1*01:01-B1*05:03* and *DQA1*02:02-B1*03:03* [106, 107]. Furthermore, other HLA class II (such as DPB1) and class I alleles have also been associated with type 1 diabetes and the search for new associations is continuing (for a review, see [107]).

The genetic aetiology is further complicated by a large number of genetic variants found to be associated with type 1 diabetes in whole-genome association studies [97, 109]. From studies of more than 60 000 people, 78 genome-wide significant regions were reported [109]. A subset of these type 1 diabetes–associated genetic variants was enriched particularly in CD4+ effector T cells. It will be important to analyse the non-HLA genetic variants for the aetiology and triggers of islet autoimmunity. Type 1 diabetes–associated common genetic variants have therefore been combined in a genetic risk score approach to make use of all the genetic information in order not only to dissect the heterogeneity of diabetes, but also the aetiology and pathogenesis of the disease. A genetic risk score was developed to distinguish monogenic diabetes from type 1 diabetes [110] or type 1 diabetes from type 2 diabetes [111]. Using 41 [112], 61 [113], or 67 [114] genetic risk variants, risk scores were developed not only to classify type 1 diabetes, but also to identify neonates with a significant risk of developing a first islet autoantibody and then progressing to clinical onset. The polymerase chain reaction (PCR) testing used is cost-effective and the type 1 diabetes genetic risk score should prove useful both in neonatal screening for children at high risk of type 1 diabetes as well as for disease classification.

Environmental aetiology

There is a long history between environmental triggers and type 1 diabetes. The first case linking type 1 diabetes to an acute viral infection was reported in the late nineteenth century when the onset of type 1 diabetes appeared to be precipitated by a mumps infection in a child [115]. Many similar reports of the clinical onset of type 1 diabetes after an acute viral infection followed [116, 117]. Taken together, these reports suggest a relation between the clinical onset of type 1 diabetes and several viruses, including rubella, mumps, coxsackievirus B, rotavirus, cytomegalovirus, and Epstein–Barr virus [117]. The true relation between these viral diseases and the clinical onset of type 1 diabetes remains conjectural. It is not until recently when longitudinal studies of children at genetic risk for type 1 diabetes have made it possible to distinguish viruses that may be aetiological and trigger islet autoimmunity from viruses that affect the pathogenesis prior to clinical onset. This distinction was made in the DAISY study, with the observation that progression from islet autoimmunity to type 1 diabetes may increase after an enterovirus infection characterized by the presence of viral RNA in blood [47]. Virus aetiology will therefore be considered only when data are reported prior to islet autoimmunity; that is, prior to the appearance of a first islet autoantibody (Figure 14.2).

Virus aetiology

Indication of virus infection prior to seroconversion includes reports by questionnaires, by direct demonstration of virus RNA or DNA by PCR, or by analysing virus antibodies as a measure of exposure. Self-reported lower respiratory tract infections in young children were associated with an increased risk of islet autoimmunity [79, 118, 119]. The IFIH1 (common SNP rs1990760) gene, interferon-induced helicase C domain–containing protein 1, was associated with the frequency of enterovirus RNA in blood [120]. Enterovirus RNA in blood did not predict islet autoantibodies, but tended to be detected at islet autoantibody seroconversion [121]. In the DIPP study (Table 14.2), stool sample enterovirus RNA using reverse transcription PCR (RT-PCR) and genotype sequencing showed that children developing islet autoantibodies had more enterovirus infections than control children. Infections occurred more than one year before the first detection of islet autoantibodies; ~50% were coxsackie A virus [122]. In the TEDDY study (Table 14.2), a large-scale investigation of known eukaryotic DNA and RNA viruses in faecally shed viruses were found to be related to islet autoimmunity. Prolonged rather than short-duration enterovirus B infections increased the risk for islet autoimmunity, in particular IAA first, in young children. In addition, early-life human mastadenovirus C infection, as well as an association with the coxsackievirus B-adenovirus receptor (CXADR), was independently correlated with a first-appearing islet autoantibody, predominantly IAA first [45]. These data were indirectly supported by enterovirus B–neutralizing antibodies in the DIPP study (Table 14.2). These antibodies are surrogate markers of coxsackie B infection in serum samples collected before and at the appearance of islet autoantibodies. Only coxsackie B1, but no other coxsackie B infections, was associated with IAA as the first-appearing autoantibody. As none of the coxsackie B antibodies was associated with the appearance of GADA, coxsackie B1 infection may contribute to the initiation of IAA-first associated islet autoimmunity [46]. The mechanisms by which persistent infection induces an autoimmune response are not understood. It may be speculated that children with HLA-DQ8 have an underperforming immune response to coxsackie B, which would explain the prolonged shedding. The neutralizing virus antibodies

may be low level or poor binders. Coxsackie B has amino acid sequence homologies to islet autoantigens [123] and molecular mimicry cannot be excluded as a possible explanation of the relationship between prolonged virus infection and the appearance of IAA.

Biomarkers of triggers

There is a paucity of studies investigating the immune response to viral infections in children with an increased genetic risk of developing islet autoimmunity and type 1 diabetes. The timing is critical and it cannot be excluded that the pattern of an autoimmune response is comparable to that of an immune response to a virus (Figure 14.6). The essential cellular reactions to establish an immune response eventually also leading to the formation of immunoglobulin (Ig)G antibodies are completed within three weeks or ~21 days. The timing of the human immune response has been detailed in studies of naturally occurring infections, such as SARS-CoV-2 [124], but more often after vaccination [125–127], and in evaluating the immune response to neoantigen bacteriophage phi X 174, a T-cell–dependent antigen [128]. Dissecting the immune response to a potential virus, such as coxsackie B, to trigger islet autoimmunity may require more frequent blood sampling than is currently achieved in longitudinal studies of children followed from birth (Table 14.2). A blood sample was at best obtained every third month. Omics biomarkers including whole-genome sequencing, epigenomics, transcriptomics, metabolomics, plasma cytokines, single-cell sorting, and single-cell sequencing will be needed to probe human immunity [125, 129]. Data from whole-blood transcriptomics in the TEDDY and DIPP studies confirmed age-associated gene expression changes in healthy infancy [130, 131], but also showed age-independent changes particularly in natural killer (NK) cells prior to either IAA first or GADA first [132]. Serum fatty acids (pentadecanoic acid, heptadecanoic acid, stearic acid, and conjugated linoleic acid), but also other factors such as amino acids and vitamin C and D [133], increased the risk for a first islet autoantibody [49, 134]. In fractionated CD4+ and CD8+ T cells and unfractionated peripheral blood mononuclear cells in the DIPP study, mRNA sequencing prior to seroconversion showed upregulation of interleukin 32 (IL-32) in activated T cells and NK cells [135]. Studies of the immune response prior to the first-appearing islet autoantibody should increase the possibility of developing novel biomarkers for the mechanisms that trigger islet autoimmunity.

Pathogenesis

The pathogenesis of type 1 diabetes is strongly associated with IAA, GADA, IA-2A, and ZnT8A biomarkers (Table 14.1). These pathogenic markers are useful to predict progression to clinical onset, but also to classify type 1 diabetes once diabetes has been diagnosed. HLA does not seem to influence the tempo of the disease process when progressing from a first to a second islet autoantibody [53, 136]. Stage 1 is reached when two or more islet autoantibodies have developed (Figure 14.2). The role of the HLA class II molecules in the immune response is to convey cell–cell interactions between T-helper (CD4+) lymphocytes and antigen-presenting cells (APCs) or B lymphocytes. The CD4+ T cell provides help to cytotoxic T lymphocytes (CD8+) as well as to B lymphocytes. It is assumed that these basic immune response mechanisms contribute to the appearance of a second, third, or fourth autoantibody.

We need to consider which factors contribute to progression from multiple autoantibodies without dysglycaemia (stage 1) and multiple autoantibodies with dysglycaemia (stage 2) to clinical onset (stage 3). First, the number of islet autoantibodies accelerates progression to stage 3 (Figure 14.3) [39, 137]. In children with persistent autoantibodies, higher IAA and IA-2A, but not GADA, levels increase the risk for stage 3 [138]. Several risk scores have been developed to predict the time to stage 3 among people with multiple islet autoantibodies [114, 139–141]. Islet autoantibodies are becoming widespread biomarkers of autoimmune type 1 diabetes in stage 1 or 2 (Figure 14.3), but need to be combined with β-cell function tests such as oral or intravenous glucose tolerance tests or continuous glucose monitoring [142–145]. Glycated haemoglobin (HbA_{1c}) was a specific but not sensitive early indicator for stage 3 type 1 diabetes diagnosed by glucose tolerance tests or asymptomatic hyperglycaemia [146, 147]. We need additional biomarkers, perhaps C-peptide and plasma glucose, to predict the time to clinical onset better in anticipation of treatment that will halt the pathogenesis at either stage 1 or stage 2 [148, 149].

Cellular autoimmunity

Stage 1 and stage 2 cellular autoimmunity has been examined in the peripheral blood in relation to the observations in the pancreas. Pancreas specimens from organ donors found to have one (pre-stage 1) or multiple islet autoantibodies (stage 1 or stage 2) have

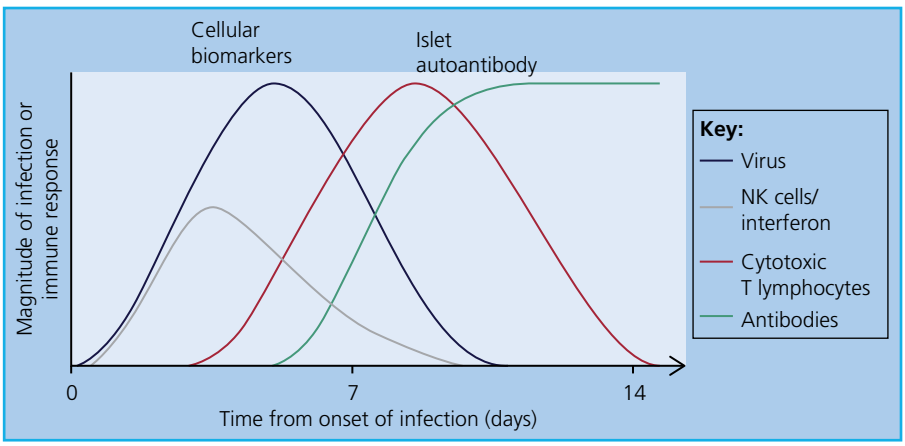

Figure 14.6 Magnitude and timing of an immune response to a common virus. It is suggested that the timing of the cellular and humoral reactions would potentially be the same for a virus that triggers islet autoimmunity. The virus may be in circulation for about 7 days. It is neutralized because of the combined immediate action of natural killer (NK) cells and interferons. Antigen-presenting cells that engulf virus-infected host cells present virus antigens on HLA class II heterodimers to be captured by the T-cell receptors of CD4+ T cells. The CD4+ T helper cells will help to activate cytotoxic CD8+ T cells and B cells. The former kill virus-infected cells, while the latter generate virus antibodies. It cannot be excluded that the islet autoimmunity response follows a similar pattern after a virus infection.

been studied [150–152]. Stage 1 pancreas had no abnormalities. Stage 2 pancreases from individuals with multiple autoantibodies and confirmed increased HLA risk showed mononuclear cell infiltrates (insulitis) in a smaller fraction of islets (<5%) and comprised predominantly CD3+ CD8+ T cells [152]. Insulin immunocytochemistry showed reduced staining and such pseudo-atrophic islets were present in multiple small foci scattered throughout the pancreatic tissue.

Single and multiple autoantibody-positive donors had relative β-cell area comparable to that of people without autoantibodies. Combining clinical features, genetic risk score, plasma C-peptide, and islet autoantibodies modelled insulitis in the absence of histological definition [150]. Factors that allow transmission from stage 1 to stage 2 and initiate insulitis remain to be identified. The identification of β-cell autoantigen-specific T lymphocytes has been challenging and the development of standardized assays of T lymphocytes specific to islet autoantigens (insulin, GAD65, and IA-2) is still difficult to achieve. Soluble HLA class II tetramer assays to assess autoantigen-specific T lymphocytes should prove useful to follow individuals transitioning between stages 1, 2, and 3 [153]. Peripheral blood cellular biomarkers may include neutrophils [154], regulatory T cell (Treg) enumeration [155], NK cell signatures [132], transcriptomic analysis of peripheral blood mononuclear cells [156], RNA sequencing of single sorted cells [157], and possibly HLA class I restricted pancreatic islet antigen peptide–specific CD8+ T cells [158]. Cellular biomarker analyses would require standardized T-cell tests that are yet to be achieved [159]. Longitudinal studies of children transitioning between stage 1, stage 2, and Stage 3 will be critical to define specific cellular factors that reflect the pathogenesis.

Humoral autoimmunity

The four major autoantigens (Table 14.1) are used in standardized assays to detect and quantify autoantibodies. The Islet Autoantibody Standardization Program (IASP) is a collaborative effort aimed at improving the performance of assays for autoantibodies that mark the pathogenesis and the concordance between laboratories [27]. The utility of islet autoantibodies has been further advanced by the European Medicines Agency (EMA), which has issued a positive qualification opinion for islet autoantibodies as enrichment biomarkers for type 1 diabetes prevention trials [160, 161].

There is a comprehensive literature on which autoantibody is thought to have the highest predictive marker for clinical onset (stage 3) [148, 162]. Although the number of islet autoantibodies is related to risk for type 1 diabetes [32, 39], additional features of the respective autoantibodies need to be considered:

- *Insulin* represents the autoantigen that has the lowest interlaboratory consistency in the IASP workshops [163]. Proinsulin autoantibodies remain to be fully characterized [164].
- *GAD65* has been tested after truncation of the N-terminal end, which increases the predictive value for type 1 diabetes compared to full-length GAD65 [27, 165–167].
- *IA-2* is present in at least two major forms, IA-2 and IA-2β. Autoantibodies to either isoform add to the ability to predict the clinical onset of type 1 diabetes [168–171]. An antigenic determinant within the N terminus of IA-2, IA-2ec autoantibodies was detected in individuals with type 1 diabetes and in a subgroup of adults with autoimmune diabetes [172].
- *ZnT8* has a major polymorphism at position 325, allowing the detection of ZnT8A variants dependent on whether tryptophan (W), arginine (R), or glutamine (Q) is present on position 325 [38, 173–176]. Most laboratories analyse both the W and R variants simultaneously and the ZnT8A predictive value is given as a combination of the two variants.

Serum samples from individuals with newly diagnosed type 1 diabetes are often tested to detect additional autoantigens. The importance of autoantibodies against additional autoantigens may improve the positive predictive value for type 1 diabetes. These autoantigens are often referred to as *minor autoantigens*, as they are usually detected at a frequency of <25% in new-onset type 1 diabetes. Tetraspanin-7 (glima38) was confirmed as an autoantigen by demonstrating binding to autoantibodies in type 1 diabetes [177, 178]. Other minor autoantigens include ICA12/SOX13 [179–181], VAMP2 [182], NPY [183], carboxypeptidase H [184], ICA69 [185], and INS-IGF2 [186].

Biomarkers of pathogenesis

HLA does not seem to be important to the pathogenesis and processes leading from stage 1 and 2 to clinical onset at stage 3 (Figure 14.2) [32, 53]. Genetic factors contributing to the pathogenesis include genes related to T-cell function (Table 14.3). Genetic risk scores, which consider genetic factors related to both aetiology and pathogenesis, have proved useful in determining the risk for individuals with autoantibodies of progressing to clinical onset regardless of whether they have first-degree relatives with diabetes or belong to the general population [111–113].

Diabetes diagnosis

The criteria for diagnosing diabetes are discussed in Chapter 2 and apply to all types of diabetes [189]. Genetic markers, such as HLA genes or any particular SNP, are of no value at the time of the diagnosis of diabetes nor during the subsequent management of people with type 1 diabetes. Typing for genetic markers and the use of genetic risk scores may become clinical practice for people who cannot be clearly classified as having type 1 diabetes or type 2 diabetes.

Islet autoantibodies are not used in routine diagnosis of diabetes, but are now recommended by the European Association for the Study of Diabetes and American Diabetes Association for people with clinical features of new-onset type 1 diabetes, as standardized islet autoantibody tests may help classify diabetes in adults, particularly where there are clinical features that overlap between type 1 diabetes and type 2 diabetes [190].

Screening for islet autoimmunity and diabetes

The understanding that HLA DR3-DQ2 and DR4-DQ8 haplotypes confer an increased risk for type 1 diabetes made it possible to use PCR-based typing methods for a very large number of newborn children to be followed for islet autoantibodies and subsequent diabetes [14, 56, 69, 70]. At-birth screening for increased genetic risk using genetic risk scores [112] has initiated primary prevention trials with oral insulin [191].

Screening schoolchildren for islet autoantibodies has been advocated as a means to prevent diabetes ketoacidosis at the time of

Table 14.3 Examples of genetic factors related either to the aetiology of islet autoimmunity or to pathogenesis leading to clinical onset of type 1 diabetes.

Genes related to aetiology			**Reference**
HLA-DQ8	IAA first	Antigen presentation	[28]
HLA-DQ2	GADA first	Antigen presentation	[28]
SH2B3	Islet autoimmunity	Immune adaptor protein	[187, 188]
PTPN22	Islet autoimmunity	Protein tyrosine phosphatase	[187]
PPIL2	Islet autoimmunity	Peptidylprolyl isomerase like 2	[187]
ERBB3	Islet autoimmunity	Erb-B2 receptor tyrosine kinase 3	[188]
INS	IAA first	Insulin gene regulatory	[187, 188]
TTC34/PRDM16	IAA first	Zn finger transcription factor	[187]
RBFOX1	GADA first	RNA binding protein	[187]
Related to pathogenesis			
INS	Type 1 diabetes	Insulin gene regulatory	[187]
RNASET2	Type 1 diabetes	Extracellular ribonuclease	[187]
PLEKHA1	Type 1 diabetes	Pleckstrin homology domain containing, family A	[187]
PPIL2	Type 1 diabetes	Peptidylprolyl isomerase like 2	[187]

GADA, glutamic acid decarboxylase autoantibody; IAA, insulin autoantibody.

clinical onset [55, 192–194]. The possibility of identifying people with multiple islet autoantibodies who could be recruited in secondary prevention trials is well established by screening first-degree relatives [149, 193, 195, 196]. Secondary prevention studies in individuals with autoantibodies have been carried out with parenteral insulin [195], oral insulin [196, 197], nasal insulin [198], GAD-alum [199], and teplizumab [149] (Chapter 76). None of the trials reached the study end-points to delay the clinical diagnosis except a trial with teplizumab. Individuals who were HLA-DR3 negative, HLA-DR4 positive, or Znt8A negative who were treated with teplizumab had fewer diabetes diagnoses than those treated with placebo [149]. The efforts to screen for islet autoantibodies in the general population as well as among first-degree relatives, perhaps in combination with improved genetic risk scores [111, 113], should help identify participants for secondary prevention trials, especially since the EMA issued a positive qualification opinion for islet autoantibodies as enrichment biomarkers in type 1 diabetes prevention trials [161].

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15 Other Disorders with Type 1 Diabetes and Atypical Phenotypes

Alice P.S. Kong[1,2,3], Elaine Y.K. Chow[1,2,3,4], Andrea O.Y. Luk[1,2,3,4], and Juliana C.N. Chan[1,2,3]

[1] Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, SAR, China

[2] Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, SAR, China

[3] Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, SAR, China

[4] Phase 1 Clinical Trial Centre, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, SAR, China

Key points

- People with type 1 diabetes classically present early, require continuous insulin treatment, and carry autoimmune markers, such as antibodies to glutamic acid decarboxylase (GAD).
- There are other types of diabetes with a phenotype that is similar to type 1 diabetes presenting with ketoacidosis, such as fulminant type 1 diabetes after viral infections or immune checkpoint inhibitor–induced diabetes.
- Other atypical forms of diabetes may have heterogeneous aetiologies, including maturity-onset diabetes of the young (MODY) and other forms of monogenic diabetes due to mutations of mitochondria or amylin or pathways implicated in pancreatic β-cell biology.
- Some people may present with ketosis-prone diabetes that reverts to a clinical course resembling type 2 diabetes after amelioration of glucotoxicity with partial recovery of pancreatic β-cell function.
- The correct diagnosis of these disorders is clinically important owing to their different clinical courses, prognosis, and management.

Diabetes is characterized by chronic hyperglycaemia due to varying degrees of insulin deficiency and resistance resulting in generalized vasculopathy in multiple body systems [1]. Insulin is the only hormone that can lower blood glucose and is key in maintaining a normal range of blood glucose between 4 and 8 mmol/l (70–160 mg/dL), irrespective of fasting and prandial states. Effective insulin activity requires insulin synthesis, processing, and secretion from a developed islet as well as peripheral action of insulin on target tissues. Effective glucose sensing is the first step of triggering insulin secretion [2], which is a highly energy-dependent process requiring normal mitochondrial function. Once hyperglycaemia develops, abnormal islet metabolism, especially that of mitochondria as the key organelle in generating energy, can lead to further impairment of insulin secretion [3]. Insulin is co-secreted with amylin, which is a key component of pancreatic amyloidosis. It has been hypothesized that hyperinsulinaemia and hyperamylinaemia, especially in the presence of insulin resistance, may contribute towards the decline in β-cell function [4]. These cellular events can interact to set up a vicious cycle of hyperglycaemia, insulin resistance, progressive insulin insufficiency, and worsening hyperglycaemia.

Genetic variants affecting these metabolic pathways can present as monogenic forms of diabetes, often associated with atypical presentation in young and normal- or low-weight individuals with a family history of diabetes [3,5]. Interactions of these pathways, modulated by cardiometabolic and inflammatory factors, can result in different trajectories in deterioration in β-cell function. Depending on the genetic predisposition, β-cell capacity, precipitating causes, and severity of hyperglycaemia, clinical presentation of diabetes can be ketotic or non-ketotic, with considerable inter-individual and intra-individual variation [6].

Apart from autoimmune type 1 diabetes, there are other causes of severe insulin deficiency that provide important insights into the pathogenesis of diabetes. Fulminant type 1 diabetes, albeit uncommon, can present at any age, characterized by rapid onset of diabetic ketoacidosis (DKA) within days, often preceded by a viral illness. These individuals typically do not have islet autoantibodies, but have very low C-peptide levels and require long-term insulin therapy [7]. More recently, the introduction of immune checkpoint inhibitors as an anti-cancer treatment has led to the recognition of autoimmune disease including type 1 diabetes as a rare adverse drug reaction [8]. These associations have revealed the complex immunomodulating roles of cytotoxic T lymphocytes (CTL), natural T-regulatory (Treg) cells, programmed death 1 (PD1) receptors, and PD1 ligands (PDL-1), which interact within a spectrum of diseases including chronic infections, cancer, and autoimmunity. While dysregulation of one of these pathways may result in a disease state (e.g. cancer), which can be modified by therapeutic manipulation, perturbation of these complex networks may result in autoimmune disease, such as type 1 diabetes [9,10].

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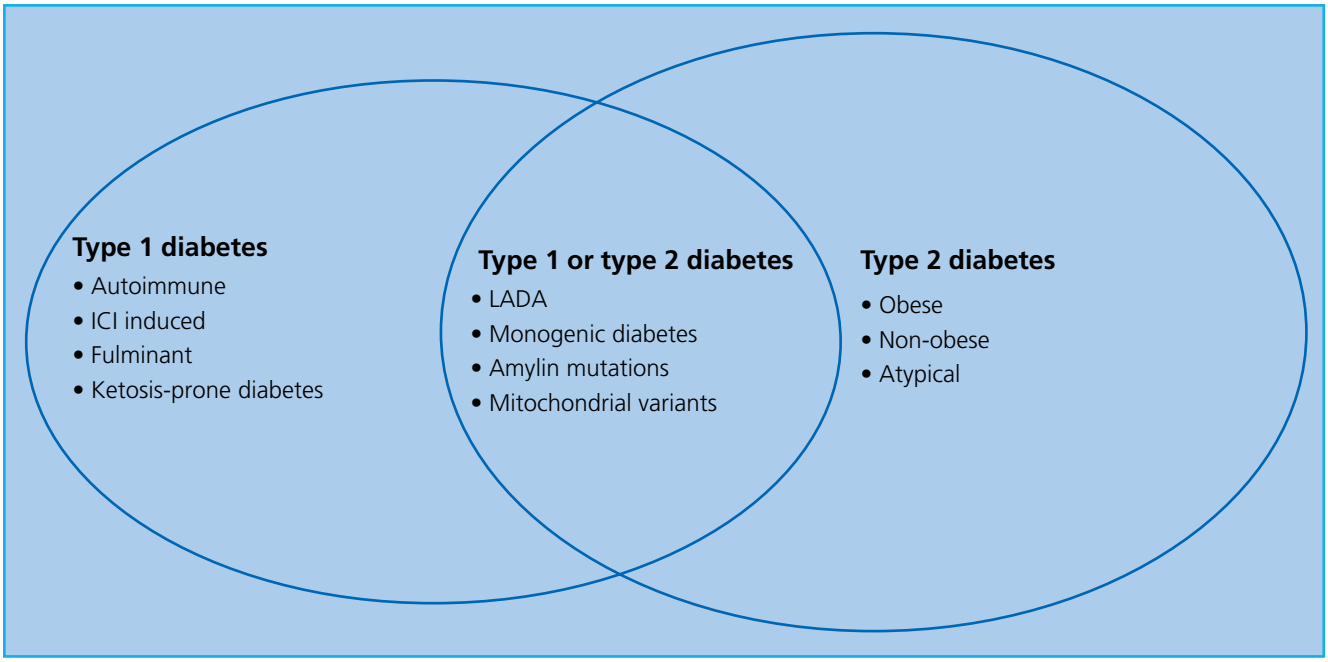

Figure 15.1 The considerable overlap between the phenotypes of type 1 diabetes and type 2 diabetes caused by complex aetiologies. Subtypes of diabetes with ketotic presentation include classic autoimmune type 1 diabetes, ketosis-prone diabetes, fulminant type 1 diabetes, and immune checkpoint inhibitor (ICI)–induced type 1 diabetes. Other subtypes of diabetes such as latent autoimmune diabetes in adults (LADA), rare variants implicated in monogenic diabetes, as well as rare and common variants implicated in other pathways associated with energy metabolism including but not limited to amylin and mitochondrial pathways might have both type 1 diabetes or type 2 diabetes presentation, depending on the co-occurrence of other familial and non-familial factors, giving each individual a unique profile that forms the basis of precision care.

Against this background, in this chapter we provide an overview of the pathogenesis, clinical features, and treatment of these atypical forms of diabetes (Figure 15.1).

Ketosis-prone diabetes

In 1980, Winter et al. first described a cohort of 129 African American young people with acute ketotic presentation, of whom 12 individuals subsequently did not require insulin and followed a clinical course resembling type 2 diabetes. These individuals were mainly young men with obesity presenting with acute hyperglycaemia and ketosis requiring insulin therapy in the acute stage. However, once acute hyperglycaemia was ameliorated, the clinical course was more akin to that of type 2 diabetes, with preserved insulin function and adequate glycaemic levels by oral glucose-lowering drugs [11].

This type of ketosis-prone diabetes or *flatbush diabetes* was relatively common in African American populations, but had also been reported as an important clinical entity in Asian and Indian populations [6]. Many of these individuals did not have human leucocyte antigen (HLA)–related genotypes or autoantibodies typical of autoimmune type 1 diabetes. Some of these individuals had obesity with insulin resistance [12]. Not uncommonly, the acute hyperglycaemic event was precipitated by sepsis made worse by consumption of sugar-sweetened beverages for thirst quenching. While the exact mechanisms underlying the initial ketotic presentation remained unknown, lipo-glucotoxicity and acute inflammatory conditions, such as infection, might compromise the β-cell function, which might already have been reduced due to other predisposing factors such as genetic causes or obesity, leading to metabolic decompensation [6].

Autoimmune diabetes in adults

In the early 1980s, among people of white European ancestry, over 90% of all individuals with diabetes diagnosed young were considered to have classic type 1 diabetes due to autoimmune islet destruction with acute ketosis and absolute insulin deficiency [13]. Autoantibodies against pancreatic islet antigens, such as glutamic acid decarboxylase (GAD), are markers for type 1 diabetes. In the early 1990s, Zimmet et al. first described a form of adult-onset autoimmune diabetes, albeit with phenotypes resembling type 2 diabetes, so called latent autoimmune diabetes in adults (LADA). In 2019, the World Health Organization (WHO) formally recognized this form of diabetes and renamed it as a slowing evolving immune-mediated diabetes of adults under the classification category of a hybrid form of diabetes, although the nomenclature of LADA is still widely used [14–16]. Individuals with LADA often carry other autoantibodies associated with coeliac disease and adrenal and thyroid disorders, suggesting it is part of a spectrum of autoimmune diseases [17]. More recent studies indicate that LADA might be a hybrid of type 2 diabetes and autoimmune diabetes. Individuals with LADA have a high frequency of both type 1 diabetes–susceptibility genotype and type 2 diabetes–susceptibility genotypes, suggesting that these aetiologies were not mutually exclusive [18,19]. In the UK Prospective Diabetes Study (UKPDS), approximately 10% of individuals with type 2 diabetes had GAD autoantibodies, the majority of whom eventually progressed to insulin dependency [20,21].

Depending on the selection criteria of clinical definition, age of diagnosis, ethnicity, and assay methodologies, the prevalence of LADA in individuals with type 2 diabetes might vary considerably. Reports from other ethnic groups suggested an estimated 10% prevalence of LADA in adult populations with a clinical presentation

of type 2 diabetes [20, 22]. In a prospective cohort of Chinese adults with young-onset diabetes, 8.1% of individuals had GAD autoantibodies suggestive of LADA. Compared to their counterparts without GAD autoantibodies, individuals with LADA were highly responsive to insulin treatment with a reduction of glycated haemoglobin (HbA_{1c}) of 2.3% (25 mmol/mol) versus 0.7% (7 mmol/mol) in individuals without LADA at 12 months. Although individuals with LADA had fewer cardiometabolic risk factors and were less likely to have cardiovascular events than their counterparts with a type 2 diabetes presentation, they were three times more likely to develop end-stage kidney disease than those with a type 1 diabetes presentation [23]. The levels of GAD autoantibodies correlate with pancreatic β-cell function. Individuals with high GAD autoantibody titre had more rapid decline in β-cell function as measured using homeostasis model assessment (HOMA2-B) and were more likely to reach β-cell failure [24].

The prompt diagnosis of LADA is clinically important, since early use of insulin was often needed to improve glycaemic levels to prevent accelerated loss of β-cell function [25]. Impaired β-cell response is often evident at diagnosis and early use of insulin might reduce the adverse effects of glucotoxicity on β cells. However, there is no evidence that early insulin implementation has any effects on the risk of late diabetes complications [26, 27]. Limited evidence suggests that treatment with sulfonylureas was associated with more rapid progression to β-cell failure, whereas treatment with dipeptidyl-peptidase 4 inhibitors might be protective [28, 29].

Apart from clinical suspicion, HLA studies might distinguish LADA from classic type 1 diabetes. In white European populations, LADA was associated with HLA DQA1-DQB1*0102(3)-*0602(3)/X, which was uncommon in individuals with typical type 1 diabetes [30]. In a consensus statement from an international expert panel, measurement of C-peptide levels as a proxy for endogenous pancreatic β-cell function was recommended to guide diagnosis and management in LADA. For C-peptide levels <0.3 and >0.7 nmol/l, individuals should be managed as type 1 diabetes and type 2 diabetes, respectively. For those in the grey zone (C-peptide ≥0.3 and ≤0.7 nmol/l), insulin should be considered in combination with other therapies to attenuate the progression of β-cell failure [31].

Fulminant type 1 diabetes

In 2000, a novel subtype of type 1 diabetes, known as fulminant type 1 diabetes, was first reported in Japan [32]. According to the Japan Diabetes Society [33], fulminant type 1 diabetes was characterized by acute destruction of β cells with rapid progression to hyperglycaemia and DKA. The pathogenesis of this disease remained to be clarified, but involvement of HLA genes and viruses has been implicated. The disease affects all ages and both sexes, including pregnant women, albeit most individuals were middle-aged men. Hence, the difference in age distribution between fulminant type 1 diabetes and autoimmune type 1 diabetes is one of the discriminating features between the two conditions.

Individuals with fulminant type 1 diabetes typically have short duration of hyperglycaemic symptoms with an average of four days, preceded by common cold–like and gastrointestinal symptoms. DKA is accompanied by near-normal HbA_{1c} despite very high plasma glucose levels, compatible with acute development of hyperglycaemia. There is seasonal variation in presentation supportive of a viral aetiology. The acute presentation of DKA is accompanied by abnormal exocrine function with increased serum levels of pancreatic enzymes (e.g. lipase, elastase-1, amylase), absent C-peptide levels, but virtually no detectable autoantibodies against constituents of pancreatic β cells. Many individuals with fulminant type 1 diabetes were reported in Japan, although sporadic cases have also been reported in other Asian countries including Korea, the Philippines, and China [34]. Given the high fatality rate of undiagnosed and untreated DKA, medical practitioners should be aware of this rare presentation, which requires intensive management, with many individuals requiring long-term insulin therapy [7].

Autoimmune type 1 diabetes and immune checkpoint inhibitors

The host immune system plays a key role in biological surveillance and defence against external and internal stressors. Among the many immune mediators, there is cross-talk between CTL and Treg lymphocytes, which results in the release of various pro-inflammatory and anti-inflammatory cytokines in response to different antigens. Although a full review of the subject is beyond the scope of this chapter, dysregulation of this immune-modulating system may result in a spectrum of conditions including chronic infection, autoimmunity, and cancer. Chronic stimulation of CTL could lead to progressive loss of cytokine production and cytotoxicity, so called T-cell exhaustion, which might promote cancer development and chronic viral infection with reduced clearance of viral load. In contrast, continuing activity of autoreactive cytotoxic cells could mediate the destruction of host tissues resulting in autoimmune diseases [9]. The immune checkpoints, PD-1 receptor and its ligand PDL-1, are immunoreceptors widely expressed in many tissues. They form part of the feedback of the cytotoxic pathway to reduce the risk of autoimmunity. Thus, while PD-1 agonists have been used to suppress adverse immune responses for the treatment of autoimmune diseases, allergy, and transplant rejection, PD-1 inhibitors have been used to augment the immune response for treatment of cancer and infectious diseases [35].

Since the introduction of PD-1 and PDL-1 inhibitors as immune-checkpoint inhibitors for treating multiple types of cancer, there have been increasing numbers of case reports of autoimmune disease as a drug-related adverse reaction. A recent systematic review and meta-analysis summarized the clinical course of 71 individuals presenting with type 1 diabetes after the initiation of immune-checkpoint inhibitor therapy. The mean age of these individuals was 61.7 years, with 55% being men and melanoma being the most frequent cancer (53.5%). Other cancer types included lung, head and neck, renal cell, and urothelial carcinoma. The median time to onset of type 1 diabetes was 49 days, with DKA presentation in 76% of the individuals. The mean HbA_{1c} was 7.8% (62 mmol/mol) at presentation. All individuals had insulin deficiency and required permanent exogenous insulin treatment, with half of the individuals having autoantibodies associated with type 1 diabetes. These latter individuals had more rapid onset and higher incidence of DKA than those without auto-antibodies [10].

There are close associations among diabetes, cancer, and chronic infection, with type 1 diabetes being rare and type 2 diabetes and cancer being common in non-Europid populations living in areas endemic for low-grade infections [36]. These intriguing observations associated with autoimmunity and immune-checkpoint inhibitors should motivate more studies to examine the interplay

among these immune-modulating pathways in both type 1 diabetes and type 2 diabetes and their associated aetiologies (e.g. acute or chronic infections) as well as subphenotypes (e.g. cancer and autoimmune disease). From a clinical practice perspective, the increasing use of immune-checkpoint inhibitors in different cancer conditions should alert healthcare professionals regarding this potential drug-related severe adverse event in the context of diabetes.

Young-onset diabetes, maturity-onset diabetes of the young, and monogenic diabetes

In people of white European descent, over 90% of individuals with diabetes diagnosed in childhood or adolescence had classic type 1 diabetes from autoimmune islet destruction with acute ketosis and absolute insulin deficiency [13]. In non-Europid populations, including those from Mexico, India, China, and the rest of Asia, classic, ketosis-prone type 1 diabetes is relatively uncommon in young adults diagnosed with diabetes. In Chinese individuals with young-onset diabetes (diagnosed before the age of 40 years), only 10% had classic type 1 diabetes. Despite the non-ketotic presentation, individuals with young-onset diabetes often required earlier insulin treatment than those with late-onset disease, while some responded well to oral anti-diabetes drugs [36]. This phenotypic heterogeneity calls for more precise diagnosis and classification to guide anti-diabetes treatment for reducing the risk of complications. In the case of monogenic diabetes with high penetrance, genetic counselling and cascade screening may be necessary for early detection and intervention among carriers of risk conferring-variants (Chapter 20) [37].

Maturity-onset diabetes of the young

Monogenic diabetes is caused by mutation in a single gene (Chapter 20). Maturity-onset diabetes of the young (MODY) is the most common form of monogenic diabetes. According to the American Diabetes Association, MODY is defined as presentation before the age of 25 years with a strong family history suggestive of autosomal dominant inheritance. It is characterized by absence of β-cell autoimmunity and sustained pancreatic β-cell function [5, 38]. In the early 1990s, some of the MODY genes were first discovered in Asian family-based cohorts of young-onset diabetes in pursuit of the underlying cause due to the low prevalence of autoimmune type 1 diabetes in these young individuals [39]. These early findings together with several large cohorts in Europe have provided the basis of the current knowledge in the field of MODY. The use of family-based linkage analysis and sequencing technology has discovered biological pathways implicated in the neogenesis, differentiation, and maturation of pancreatic β cells as well as intracellular signalling mechanisms underlying insulin sensing, synthesis, secretion, and processing as important causes of MODY [40].

Around 40 subtypes of monogenic diabetes have been identified, with variants in 14 genes being best described in the literature. These include six genes encoding proteins that, respectively, correspond to MODY subtypes 1–6: hepatocyte nuclear factor *(HNF) 4α* (*HNF4α*); glucokinase (*GCK*); HNF1α (*HNF1α*); pancreatic and duodenal homeobox 1 (*PDX1)*; HNF1β (*HNF1β*); and neurogenic differentiation 1 (*NEUROD1*). Another eight genes have been identified as possibly causative in MODY subtypes 7–14, including Kruppel-like factor 11 (*KLF11*); carboxyl ester lipase (*CEL*); paired box–containing gene 4 (*PAX4*); insulin (*INS*); B-lymphocyte kinase (*BLK*); adenosine triphosphate (ATP)–binding cassette; sub-family C (CFTR/MRP) member 8 (*ABCC8*); potassium channel, inwardly rectifying subfamily J, member 11 (*KCNJ11*); and adaptor protein, phosphotyrosine interaction, PH domain, and leucine zipper containing 1 (*APPL1*) [5]. There is now a trend to replace the old nomenclature of MODY1 and MODY 2 with *HNF4α*-MODY or *GCK*-MODY for better clarity. Most of the monogenic diabetes genes are transcription factors implicated in pancreatic β-cell development, structure, and function, such as *Pax6*, *Nkx2-2*, *Nkx6-1*, and *Pax-4* [41, 42]. Others are transmembrane channels implicated in insulin secretion, such as Kir6.2 *(KCNJ11)* and SUR1 *(ABCC8)* [5, 38, 43]. These rare variants in transcription factors typically cause significant insulin insufficiency and hyperglycaemia, with strong familial inheritance and full penetrance (Figure 15.2).

Recently, more mutations associated with monogenic diabetes have been identified [44] and the list is expected to grow with the increasing availability of DNA sequencing. Some mutations are extremely rare or associated with syndromic features (e.g. deafness, visual impairment, development abnormality). Rare variants aside, genome-wide association studies have revealed a high frequency of common variants of some MODY genes, especially in Asian populations, including *HNF1α*, *HNF1β*, *GCK*, and *PAX4*. These genetic variants might interact with other genetic, environmental, or lifestyle factors to increase the risk of diabetes or related traits [42, 45–47]. These results are in keeping with epidemiological analysis indicating the important role of abnormal β-cell biology in the pathogenesis of type 2 diabetes in Asian populations undergoing rapid transition, with obesity as a major risk factor [48].

Given the mixed phenotypes, it can be challenging to distinguish individuals with MODY from the large number of individuals with type 1 diabetes or young-onset type 2 diabetes. It is estimated that more than 80% of cases of MODY are not diagnosed or are misclassified in clinical practice [49, 50], not least because the costs of genetic analysis can be prohibitive for widespread screening for mutations in individuals with diabetes. In 2008, a consensus group recommended clinical criteria for MODY testing that included onset of diabetes below 25 years, parental history of diabetes, non-insulin dependence (for *HNF1α*- and *HNF4α*-MODY), and fasting plasma glucose of 5.5–8.0 mmol/l and HbA_{1c} <8% (64 mmol/mol) for *GCK*-MODY [51]. These criteria have high specificity but low sensitivity, with other forms of familial monogenic diabetes yet to be discovered. By extending the screening criteria to individuals diagnosed under the age of 30 years or with C-peptide positivity after three years of diagnosis (random or glucagon-stimulated C-peptide ≥0.2 nmol/l), more positive cases have been diagnosed [52]. Common variants near the *HNF1α* gene influence the levels of high-sensitivity C-reactive protein (hsCRP) in healthy populations [53] and low levels of hsCRP may distinguish *HNF1α*-MODY from type 1 diabetes and type 2 diabetes with increased sensitivity up to 90% when combined with clinical criteria [54].

In cohorts with clinical features of MODY and depending on additional selection criteria, such as C-peptide or autoimmune markers to prioritize diagnostic testing, the proportions of young individuals with monogenic diabetes might range from less than 10% to more than 50% [5, 38]. In most cohorts, over 70% of confirmed individuals with MODY had mutations in *HNF1α*, *GCK*, and *HNF1β*. In a consecutive cohort of unrelated Chinese

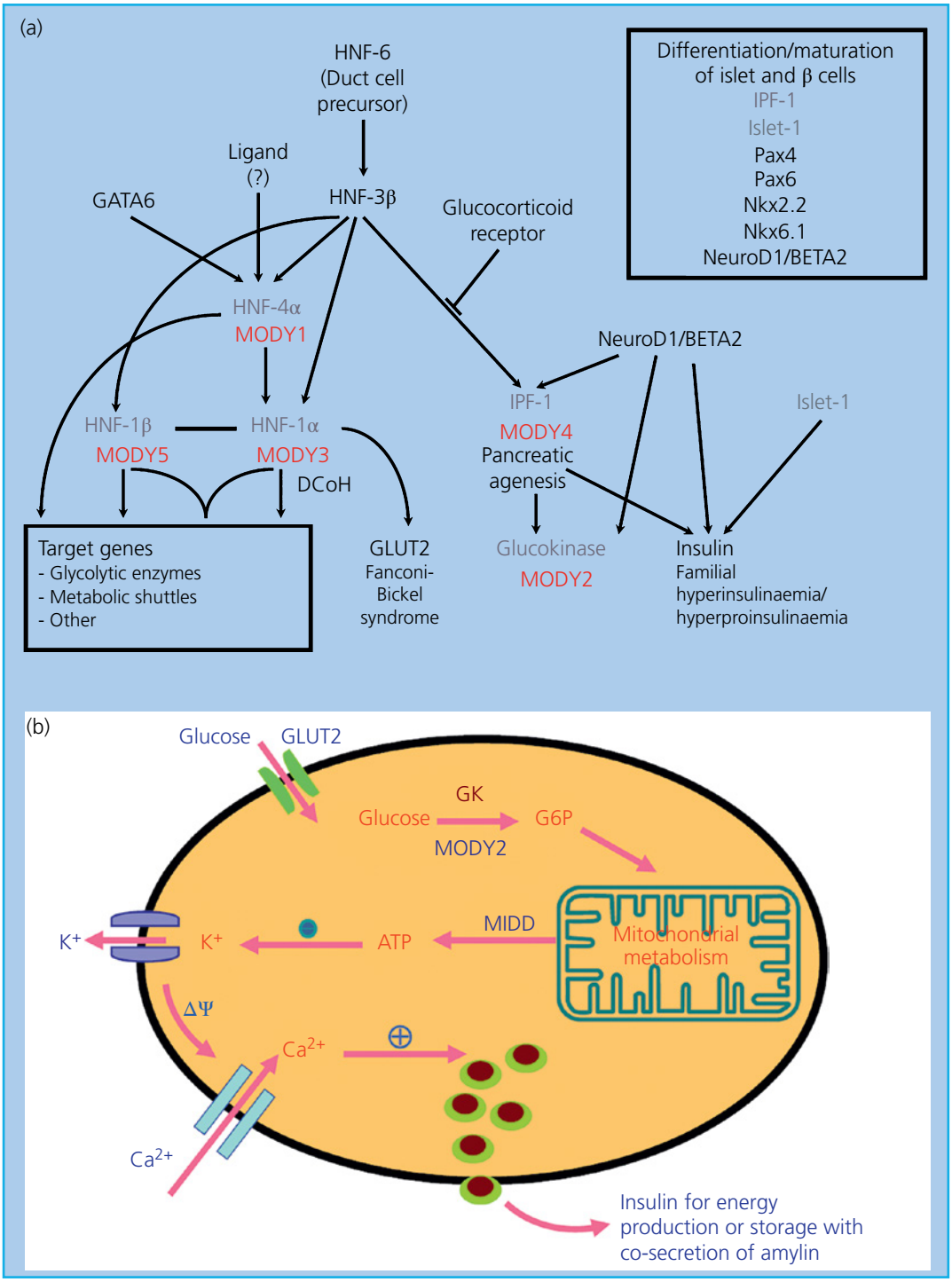

Figure 15.2 (a) The cascade of transcription factors involved in pancreatic development as well as neogenesis, differentiation, and maturation of pancreatic *β* cells. Maturity-onset diabetes of the young (MODY) includes subtypes with mutations in transcription factors, namely MODY 1 with mutations of hepatic nuclear factor (*HNF-4α*); MODY 3: *HNF-1α*; MODY 4: insulin promotion factor (*IDF-1*); MODY 5: *HNF-1β*; MODY 6: neurogenic differentiation 1 (*NeuroD1*); and MODY 7: carboxyl ester lipase (*CEL*). Other genes include glucokinase, the glucose sensor (MODY 2), glucose transporter 2 (*GLUT2*), and additional transcription factors such as *GATA*, the family of *PAX* genes, *Nkx 2.2* and *Nkx 6.1*, and neurogenin-3 (*Neurog3*). These genes interact at different stages to control islet cell development and regulate glucose sensing and insulin secretion in order to maintain a normal range of blood glucose of 4–8 mmol/l at all times, irrespective of fasting and prandial states. (b) The multiple steps involved in regulation of insulin secretion, commencing with sensing of ambient blood glucose level by glucose transporter 2 (GLUT2), glycolysis by glucokinase (GK), and adenosine triphosphate (ATP) production by mitochondria. The generated ATP particles then close the potassium channels, leading to membrane depolarization and opening of calcium channels. The intracellular calcium influx is associated with translocation of insulin- and amylin-containing vesicles to the cellular surface for extracytosis. During these processes, transcription factors are also activated, resulting in insulin gene transcription and production to replenish the insulin-containing vesicles to ensure continuous insulin supply for rapid release on demand. MIDD, maternal-inherited diabetes and deafness.

individuals with type 2 diabetes diagnosed before the age of 40 years, 5–10% had *GCK* or *HNF1α* mutations [55]. There are relatively few MODY cohorts in African, Arabic, or Latin American populations. Given the known differences in genetic, ecological, and cultural factors, different patterns of MODY might be expected [5,38]. Recently, a work group has reported good discriminatory performance of MODY risk calculators, although their applicability in non-Europid populations remains uncertain [56].

There are few cohort studies on monogenic diabetes in the USA and an estimated 95% of cases might be misdiagnosed as type 1 diabetes or type 2 diabetes [38]. In the latest analysis of a multiethnic cohort of young people under the age of 20 years with a clinical diagnosis of type 2 diabetes, whole-exome sequencing was performed to discover genetic variants associated with MODY genes classified as likely pathogenic (LP) or pathogenic (P) according to current guidelines [57]. Among 3333 participants, 93 (2.8%) carried an LP/P variant in *HNF4α* (n = 16), *GCK* (n = 23), *HNF1α* (n = 44), *PDX1* (n = 5), *INS* (n = 4), or *CEL* (n = 1). Compared with those with no LP/P variants, young people with MODY had a younger age at diagnosis and lower fasting C-peptide levels. They were also less likely to have hypertension and had higher high-density lipoprotein (HDL) cholesterol levels. Among these 2.8% of young people with clinically diagnosed type 2 diabetes, the diagnosis of MODY through sequencing would have changed clinical management in 89% of them. However, there were no clinical criteria that could reliably separate MODY from other forms of diabetes, which calls for new tools and algorithms to select individuals for genetic testing.

Accurate diagnosis of MODY has implications for choices of treatment. Typically, *GCK*-MODY is characterized by mild fasting hyperglycaemia and might not necessitate treatment. Individuals with MODY due to *HNF4α* and *HNF1α* mutations are sensitive to sulfonylureas. These individuals also respond well to incretin-based therapy with dipeptidyl peptidase 4 inhibitors and glucagon-like peptide 1 receptor agonists [5,58]. Many individuals with transcription factor MODY eventually require insulin due to progressive *β*-cell failure, often due to factors such as delayed diagnosis, long disease duration, and suboptimal glycaemic levels with ongoing glucolipotoxicity and inflammation [59].

Timely recognition of MODY also influences antenatal care, as maternal–offspring genotype concordance or discordance affects the pregnancy outcome. Using *GCK*-MODY as an example, intensive insulin treatment in an affected mother during pregnancy might result in low birth weight of affected offspring, who require a higher fasting plasma glucose to trigger insulin secretion. By contrast, high fasting hyperglycaemia in an affected mother might lead to high birth weight in an unaffected offspring due to fetal hyperinsulinaemia [59,60]. Although individuals with some MODY subtypes (e.g. *GCK*-MODY) run a mild clinical course and rarely develop complications, depending on the coexistence of other risk factors and genotypes, individuals with MODY might exhibit marked heterogeneity in terms of insulin insufficiency, complications, and treatment requirements, even among family members carrying the same variant [61,62].

Precise diagnosis, classification, and treatment are particularly important in young individuals with type 2 diabetes presentation. In Chinese people, young-onset diabetes is associated with a 1.5–6-fold increased risk of hospitalization with acute or chronic complications, cardiovascular–renal complications, and premature death, in part due to long disease duration and poor risk factor management [63,64]. The insidious nature of these symptoms might lead to delayed presentation with complications, while early diagnosis through screening of family members on identification of an index individual might prevent these adverse outcomes [61,65]. With the rising prevalence of young-onset diabetes especially in low- and middle-income countries [36], healthcare professionals need to appreciate the multiple aetiologies that might coexist in an individual with an atypical presentation of diabetes. In these individuals, precision diagnosis can have important implications for treatment selection, with some benefiting from early insulin treatment (e.g. LADA) and others from oral glucose-lowering drugs (e.g. MODY) (Table 15.1 and Figure 15.3).

Table 15.1 Clinical features, pathophysiology, and treatment implications of the 14 subtypes of maturity-onset diabetes of the young (MODY) due to rare mutations that often follow a Mendelian mode of inheritance with full penetrance.

Main defects in glucose metabolism	MODY gene mutation	Implications in choices of anti-diabetes treatment
Pancreatic islet and *β*-cell development	*HNF4α*	Sulfonylureas
	HNF1α	Sulfonylureas
	PDX1	Diet, oral anti-diabetes drugs, or insulin
	HNF1β	Insulin
	NEUROD1	Oral anti-diabetes drugs or insulin
	KLF11	Oral anti-diabetes drugs or insulin
	PAX4	Diet, oral anti-diabetes drugs, or insulin
Glucose-sensing defect	*GCK*	Diet only, no need for any drugs
Insulin secretion defect	*BLK*	Diet, oral anti-diabetes drugs, or insulin
	APPL1	Diet, oral anti-diabetes drugs, or insulin
Insulin gene defect	*INS*	Oral anti-diabetes drugs or insulin
Adenosine triphosphate (ATP)-sensitive potassium channel dysfunction	*ABCC8*	Sulfonylureas
	KCNJ11	Oral anti-diabetes drugs or insulin
Pancreas endocrine and exocrine dysfunction	*CEL*	Oral antidiabetes drugs or insulin

Source: Adapted from Urakami 2019 [5].

Mitochondrial gene mutations

Mitochondria are important intracellular organelles in maintaining glucose homeostasis and energy balance. Mitochondria have their own genome and unlike nuclear DNA, which is protected by histones, mitochondrial DNA is more vulnerable to oxidative stress and environmental toxins. Superoxide radicals generated by the mitochondrial respiratory chain are major sources of damage to mitochondrial DNA. Older people with a positive family history of diabetes have a high frequency of mitochondrial mutations [66]. Due to its maternal inheritance, mitochondrial DNA is a well-known cause of a subtype of maternally-inherited diabetes mellitus [67].

In 1992, an A3243G mutation in the mitochondrial DNA coding for $tRNA^{Leu(UUR)}$ (mt3243) was first reported. This mutation was

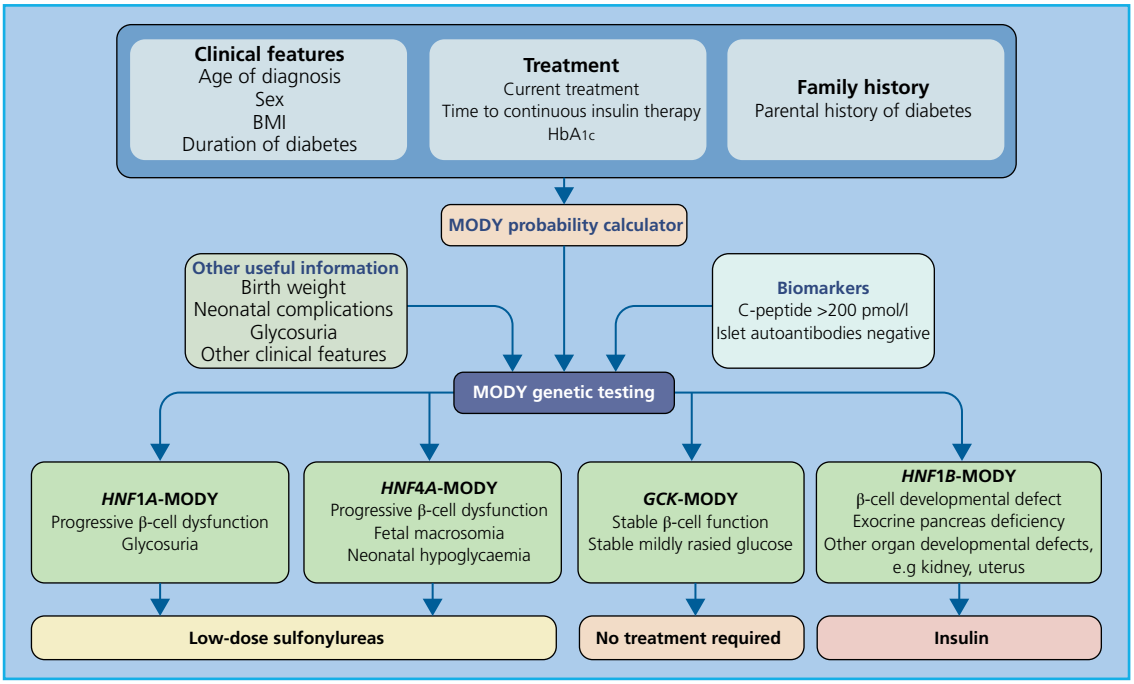

Figure 15.3 A proposed algorithm for identifying individuals with monogenic diabetes and targeted treatment. BMI, body mass index; HbA_{1c}, glycated haemoglobin; MODY, maturity-onset diabetes of the young, maturity-onset diabetes of the young. Source: Adapted from Hattersley and Patel 2017 [58].

found in individuals with type 1 diabetes and type 2 diabetes presentations, and is characterized by maternal inheritance and deafness [68]. The prevalence of this mutation has been reported to be 1–3% in Chinese individuals with diabetes with either ketotic or non-ketotic presentation [69–71]. Other point mutations associated with increased risk of diabetes include sites at 3316, 3394, and 14 577, as well as deletion and rearrangement in mitochondrial DNA [66].

In keeping with its candidacy as a *thrifty gene*, common polymorphisms of the mitochondrial DNA (T16189C) have been associated with increased risk of metabolic syndrome in Chinese people, after adjustment for age and body mass index, with a frequency of 44% compared with 33% in those without metabolic syndrome [72]. In a meta-analysis, Asian people without diabetes had a higher frequency of the T16189C variant than their European counterparts (31.0% versus 9.2%) [73]. Despite negative reports in European populations [73], there are consistent data showing a risk association of the T16189C variant with type 2 diabetes in Asian populations [74,75]. There are major inter-ethnic differences in mitochondrial haplotypes, with different mitochondrial variants or haplotypes associated with type 2 diabetes in Indian [76], Turkish [77], and Chinese Uyghur [78] populations.

Given the pivotal roles of mitochondria in maintaining islet biology and energy metabolism, mitochondrial diabetes might be an important cause of diabetes in populations undergoing rapid transition in terms of energy consumption [79,80]. Using transcriptomic and proteomic analyses, researchers had reported changes in multiple genes and proteins in non-obese, non-dyslipidaemic diabetes mouse islets with upregulation of glycolysis and gluconeogenesis pathways, downregulation of oxidative phosphorylation pathways, impaired glucose-induced NADH and ATP production, as well as reduced oxidative and glycolytic glucose metabolism. These data suggest that hyperglycaemia *per se* might induce metabolic changes in β cells that could markedly reduce mitochondrial metabolism and ATP synthesis to drive progressive failure of β cells in diabetes [3].

Taken together, in predisposed individuals, genetic or non-genetic factors that perturb glucose homeostasis might trigger and perpetuate a series of events culminating in persistent and worsening hyperglycaemia. These interlinking events emphasize the importance of maintaining euglycaemia to reduce the risk of onset and worsening of hyperglycaemia in predisposed individuals [3].

Pancreatic amyloidosis and other pancreatic diseases

Amylin, a 37-amino-acid polypeptide, is co-secreted with insulin by pancreatic β cells. It is the principal constituent of the amyloid deposits in the islets of Langerhans in type 2 diabetes [81,82]. In autopsy series, pancreatic amyloidosis was associated with β-cell loss in both white European and Chinese individuals [83–85]. Using pancreatic specimens, Asian researchers found significant correlations between body mass index and volume of β cells [86], with amyloidosis, inflammation, and fibrosis as common pathological features [87]. Formation of intracellular islet amyloid polypeptide oligomers causes pancreatic β-cell loss with progressive hyperglycaemia [82]. Changes in metabolic milieu or genetic variants encoding proteins involved in amylin metabolism might lead to structural changes of amylin and increased oligomerization with β-cell death [88]. One example is the S20G variant of the amylin gene, which enhances cytotoxicity in one transformed cell line (COS-1) and amyloidogenicity *in vitro*. This genetic variant is found in 2–3% of Japanese, Chinese, and Pacific Islanders with diabetes. In Taiwanese Chinese, normoglycaemic carriers of the S20G variant have reduced early-phase insulin secretion. However, results of co-segregation analysis in family studies of the S20G variant were inconclusive, suggesting that this genetic variant is likely to be a risk-modifying factor rather than a major diabetes gene [4,65].

In India, young-onset type 2 diabetes often overlaps with monogenic forms of diabetes, fibrocalculous pancreatic diabetes, and diabetes associated with malnourishment [89]. In Indian individuals with tropical calcific pancreatitis, the loss of endocrine function accompanying the exocrine damage might be an additional factor contributing to the clinical manifestation of diabetes in the presence of other stressors [90].

Interpretation of genetic variants in the era of sequencing

The increasing availability of DNA sequence data and access to sophisticated bioinformatic algorithms mean that an unbiased bioinformatics-based assessment of the predicted impact of a genomic variant is rapidly available. However, there are potential pitfalls of variant classification based on bioinformatics analysis alone. In a recent study using bioinformatic algorithms, 88 *likely pathogenic* monogenic diabetes variants were identified in 80 individuals (8.6%) from a cohort of 1019 individuals with type 1 diabetes for 50 or more years. Using the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) standards and guidelines, only 9 of these 88 variants were classified as likely pathogenic or pathogenic variants. Other published research studies with an over-reliance on *in silico* prediction tools also reported high levels (~90%) of false-positive likely pathogenic monogenic diabetes variants. Given the complex nature of diabetes with multiple aetiologies, additional information is needed to interpret the predicted effect on protein function. This includes knowledge regarding the gene–disease validity, mode of inheritance, appropriate allele frequency cut-off thresholds, most clinically relevant transcript, and specificity of disease-causing variant type for each gene [91].

In this context, a good understanding of human biology, epidemiology, and clinical medicine is essential in integrating the exponential growth of information available from a single individual with or at risk of having diabetes. Given the importance of genetics in the pathogenesis of diabetes, using family members to ascertain co-segregation of novel genetic variants with diabetes and related traits is one approach where physicians can verify their clinical relevance. Moreover, additional aetiologies and disease-modifying factors need to be considered. Apart from autoimmune markers as well as common and rare variants of the nuclear and mitochondrial genome, other genetic, epigenetic, and non-genetic familial factors can be important. For example, epidemiological studies have reported increased risk of diabetes with haemoglobinopathies (e.g. thalassaemia traits) due to increased iron turnover with oxidative stress and β-cell dysfunction [92,93]. People with chronic hepatitis B and C infections have increased risk of diabetes due to low-grade inflammation [94,95]. Other non-modifiable factors, such as age, sex, and disease duration, as well as modifiable factors, such as cognitive-psychological-behavioural factors, management of cardiometabolic risk factors, concomitant medications, access to care, and timeliness in diagnosis and treatment to preserve β-cell function are important considerations in improving the precision of diagnosis and treatment (Figure 15.4) [1,36,37,44,96].

Conclusion

Until recently, autoimmune type 1 diabetes was considered to be the predominant form of diabetes in children and young adults. Clinical and molecular epidemiological analysis has discovered multiple genetic or acquired factors, which may affect islet and mitochondrial biology, with considerable overlap between type 1 and type 2 diabetes phenotypes. Detailed medical history taking, complete physical examination, and use of appropriate laboratory testing along with evaluation of autoimmune and genetic markers may help clinicians improve the precision of diagnosis and management of individuals with atypical diabetes for better outcomes.

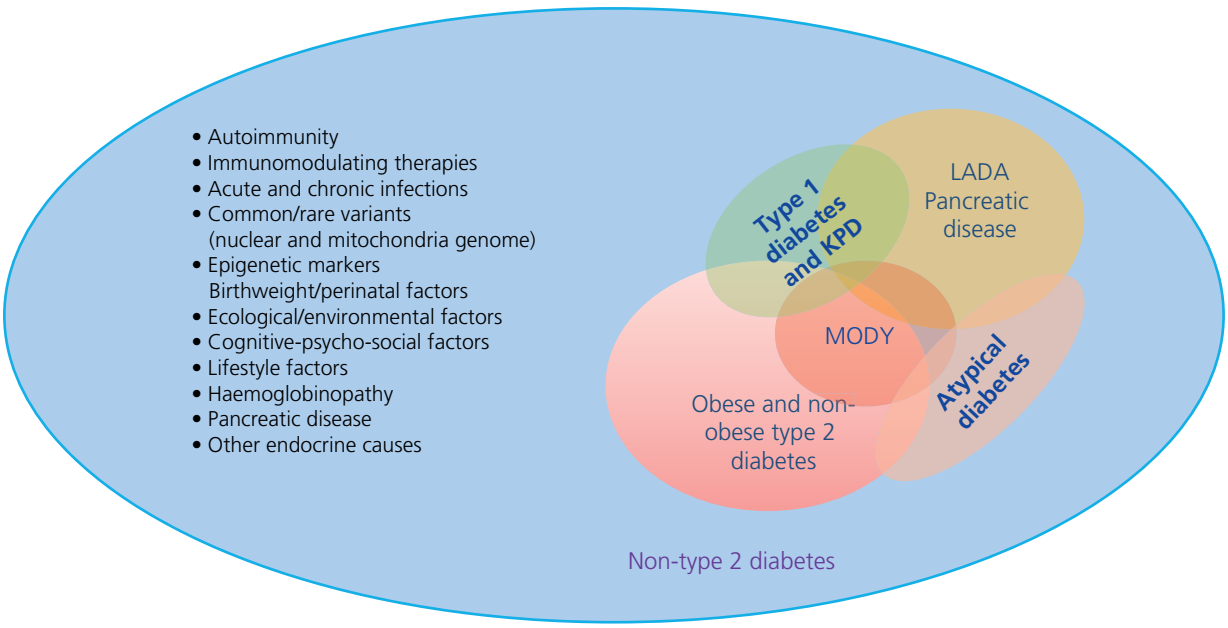

Figure 15.4 The complex aetiologies in diabetes with genetic and non-genetic causes, which interact giving rise to a diversity of clinical presentation, trajectories, and outcomes. KPD, ketosis-prone diabetes; LADA, latent autoimmune diabetes in adults; MODY, maturity-onset diabetes of the young.

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16 Abnormalities of Insulin Secretion and β-Cell Defects in Type 2 Diabetes

Stefano Del Prato, Cristina Bianchi, and Giuseppe Daniele
Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Key points

- Type 2 diabetes is a heterogeneous, progressive disease caused by the interaction of genetic and environmental factors, which adversely affect β-cell function and tissue insulin sensitivity.
- Physiological regulation of insulin secretion is controlled through a sophisticated integrated process encompassing finely tuned feedback mechanisms between the β cell, plasma glucose and other nutrient levels, insulin sensitivity, incretin hormones, neuropeptides, and neuronal control.
- β-cell abnormalities are the main determinant of the rate of progression of type 2 diabetes. Worsening of the ability of the β cells to compensate for existing tissue insulin resistance sets the rate of progression of the disease.
- A predisposing genetic background is the most likely explanation for the evidence provided by multiple studies that β-cell function is altered well before the onset of overt type 2 diabetes.
- In predisposed normoglycaemic individuals, loss of first-phase insulin secretion and loss of glucose sensitivity, i.e. the ability of β cells to sense and respond properly to changes in glucose concentrations, represent the earliest abnormalities of β-cell function.
- An apparent reduction in β-cell volume of up to 60% has been found in people with pre-diabetes, with a further reduction in individuals with overt diabetes. The decrease in β-cell mass is the result of an increased rate of apoptosis, autophagy, and dedifferentiation. The increased β-cell death occurs without a compensatory increase in β-cell replication owing, at least in part, to the limited regenerative capacity of adult human β cells.
- Multiple factors contribute to the progressive loss of β-cell function and β-cell mass, including the characteristic alterations of the metabolic milieu of type 2 diabetes, i.e. hyperglycaemia, hyperlipidaemia, chronic β-cell stimulation, and impaired incretin effect.
- All factors that accelerate the decreased number and function of β cells promote common damage pathways, including oxidative stress, endoplasmic reticulum stress, inflammation, immune system activation, and amyloid deposition. These factors impair both the function and survival of β cells, although abnormalities of β-cell function seem to be predominant compared with the reduction in the number of insulin-secreting cells.
- Preserving β-cell function is key to ensuring long-term glycaemic management in people with type 2 diabetes.

Type 2 diabetes is a complex, progressive disease. In the past 40 years or so, several alterations involving different tissues have been identified as contributing to the development and progression of hyperglycaemia and concomitant metabolic disorders [1,2]. Of the many pathogenic mechanisms, insulin resistance and impaired β-cell function remain the hallmarks of the condition. Insulin resistance is almost universally present in people with type 2 diabetes and it is already apparent in predisposed individuals. However, normal glucose tolerance is maintained in the face of insulin resistance provided that the β cell remains capable of compensating for the increased secretory demand. This simple observation highlights how the defect of insulin secretion plays a central role in the development of glucose intolerance, conversion to diabetes, and progression of the disease. Insulin secretion, indeed, is key to the maintenance of glucose homeostasis.

Physiological insulin secretion

Insulin is secreted from the β cells of the pancreas. The insulin-producing cells are embedded in ~3 million islets of Langerhans scattered throughout the exocrine pancreatic tissue, where they account for up to 60% of the entire islet cell population. The total β-cell weight of a normal-weight adult does not exceed 1 g. This minute β-cell mass contains sufficient insulin to ensure up to 8–10 days of hormone requirement [3]. Insulin is key for keeping daily plasma glucose concentration within a tight range in spite of wide fluctuations in carbohydrate intake (i.e. food ingestion) and demand (e.g. resting conditions vs physical activity). This implies tightly regulated, dynamic, and rapidly acting feedback between insulin secretion and plasma glucose concentration [4].

Glucose is actively transported inside the β cell in a linear manner with plasma glucose levels through the activity of glucose transporter 2 (GLUT2). Once inside the cell, glucose is promptly phosphorylated by glucokinase, allowing its entry into the glycolytic pathway ending with the generation of adenosine triphosphate (ATP), the main driver of glucose-induced insulin secretion. Increased cytosolic ATP levels cause the closure of ATP-sensitive K^+ channels and depolarization of the plasma membrane, causing the opening of the voltage-dependent Ca^{2+} channels and Ca^{2+} influx. The rise in intracellular Ca^{2+} concentration triggers the

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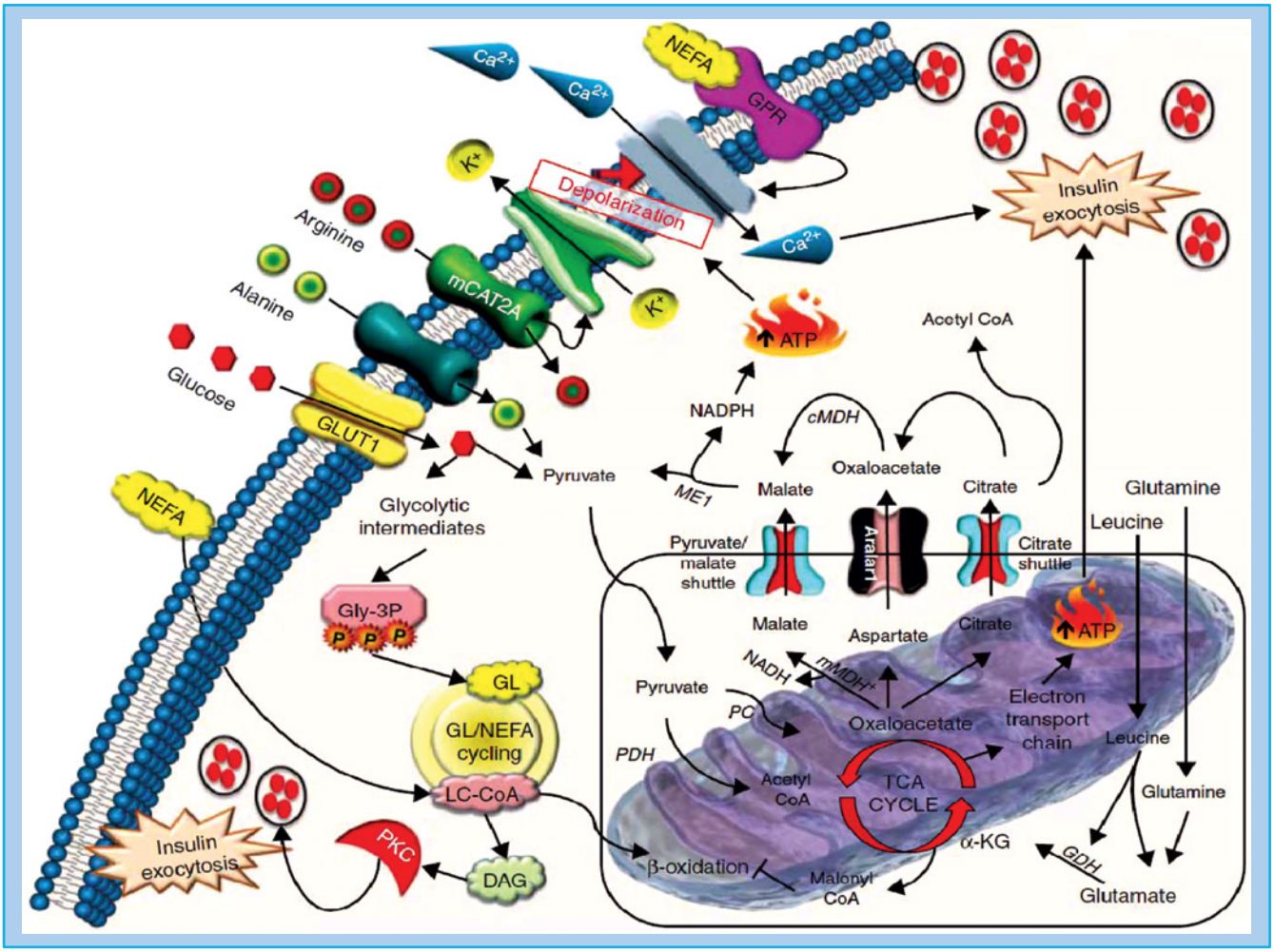

Figure 16.1 Mechanisms of nutrient stimulus–secretion coupling in the pancreatic β cell. ATP, adenosine triphosphate; cMDH, cytoplasmic malate dehydrogenase; CoA, coenzyme A; DAG, diacylglycerol; GDH, glutamate dehydrogenase; GL, glycerolipid; GLUT1, glucose transporter 1; GPR, G-protein–coupled receptor; LC-CoA, long-chain fatty acids acyl coenzyme A esters; NEFA, non-esterified fatty acids; PC, pyruvate carboxylase; PKC, protein kinase C; TCA, tricarboxylic acid. Source: Newsholme et al. 2014 [5].

exocytosis of insulin granules and the release of insulin (Figure 16.1). Therefore, glucokinase is the rate-limiting step for the glycolytic flux and represents the main glucose sensor in the β cell, although recent experimental work has suggested the existence of additional sensing systems, including heterodimers of sweet taste receptors [6].

Insulin secretion in response to glucose is biphasic in nature, with a short-lasting (a few minutes) first-phase increase in insulin secretion followed by a more sustained second-phase increase, which lasts as long as glucose levels remain elevated [7,8]. The biphasic response of insulin secretion reflects the dynamics of spatially and functionally distinct intracellular insulin granule pools. According to this view, first-phase insulin secretion reflects fusion to the cell membrane of pre-docked granules from a readily releasable granule pool [9]. This pool accounts for no more than 5% of the total granules in the cell. The increase in ATP concentration in the β cell on exposure to glucose facilitates movement of insulin granules and priming of exocytosis. The second phase of insulin secretion involves the recruitment of granules from a more distant and larger reserve pool as well as stimulation of *de novo* insulin synthesis [10]. This characteristic biphasic response of the β cell can be clearly appreciated using the hyperglycaemic clamp technique depicted in Figure 16.2 [11]. A square wave of hyperglycaemia is obtained with this technique, which distinguishes the first phase of insulin secretion, which is generally dependent on the magnitude of the early increase in glucose levels, and the second phase. Although such a clear-cut distinction is not fully apparent with a more gradual glucose increase, the same sequence – that is, an early insulin response followed by a more sustained response – occurs after the ingestion of carbohydrates or a regular meal.

Insulin is secreted into the portal vein and exerts an immediate biological action on the liver. In the fasting state, portal insulin limits the supply of glucose from the liver into the systemic circulation to match the need of glucose-dependent tissues, primarily the central and peripheral nervous system and red blood cells. Basal insulin secretion is characterized by rapid oscillations with a 3–4-minute frequency [12]. In the absorptive state, insulin is secreted in proportion to the increments in plasma glucose levels on the entry of nutrients into the circulation following food digestion and absorption. The route of administration of glucose and other nutrients markedly influences insulin secretion. When glucose is administered via the gastrointestinal tract, a much greater stimulation of insulin secretion is observed compared with similar plasma glucose levels obtained with intravenous glucose infusion.

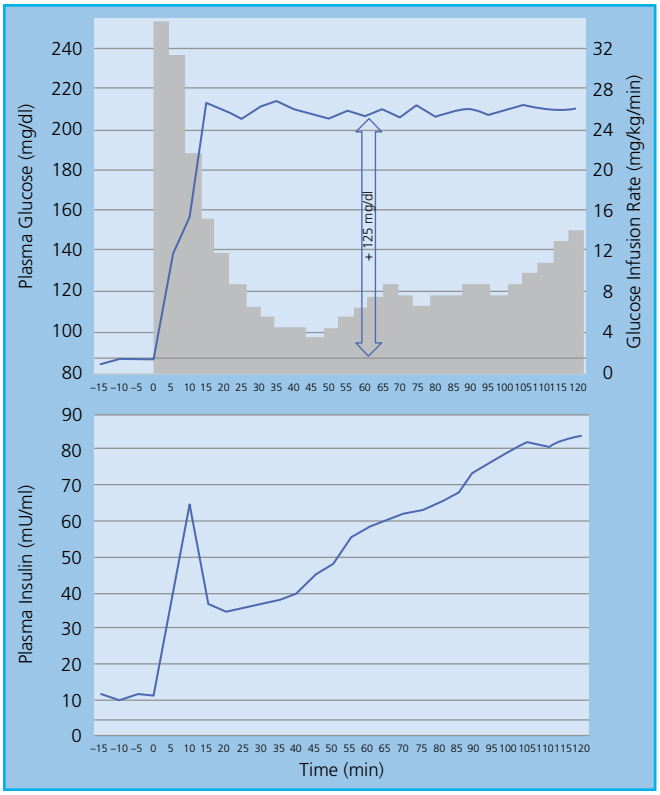

Figure 16.2 First- and second-phase plasma insulin response during hyperglycaemic clamp in healthy individuals. Plasma glucose is acutely raised +125 mg/dl (6.9 mmol/l) above baseline and maintained for the ensuing two hours. Plasma insulin concentration is measured at regular intervals. Source: DeFronzo et al. 1979 [11]. Reproduced with permission of the American Physiological Society.

This difference in insulin secretion between intravenous and oral glucose administration is referred to as the *incretin effect* [13] and it is mediated by the release of gastrointestinal hormones. The major incretin hormones in humans are glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) and these contribute to the maintenance of glucose homeostasis after meals [14]. Other gut hormones, such as cholecystokinin (CCK), contribute to the incretin effect, although the importance of these peptides is negligible under physiological conditions [15].

Insulin secretion is also stimulated by protein and fat ingestion [16]. Amino acids trigger insulin release and amplify insulin-secretory pathways by acting as a substrate for the tricarboxylic acid cycle and/or redox shuttles with subsequent generation of ATP, and through direct depolarization of the plasma membrane (Figure 16.1). The latter is the consequence of the transmembrane transport of positively charged amino acids via specific amino acid transporters and Na^+ cotransport. Lipids and free fatty acids play a crucial role in β-cell function and insulin release [5]. In the presence of nutrients, free fatty acids modulate insulin secretion through three distinct pathways:

- Tricarboxylic acid cycle/malonyl-coenzyme A (CoA) metabolic signalling.
- Glycerolipid/free fatty acid cycling.
- Direct activation of G-protein–coupled receptors (GPCRs) [5].

Finally, many other factors, including neuropeptides and neuronal control, contribute to the modulation of insulin secretion through a sophisticated integrated process [5]. Stimulation of the parasympathetic nervous system increases insulin secretion [17] while sympathetic stimulation exerts an inhibitory effect [18].

The pancreatic islets of Langerhans are more than just the home of the insulin-producing β cells. They contain several additional endocrine cell types, most notably glucagon-producing α cells and somatostatin-producing δ cells, which coordinate their activity in response to changes in glucose and other nutrients and modulate β-cell activity through a paracrine crosstalk between the three major endocrine cell types of the islet [19]. At the systemic level glucagon functionally opposes the glucose-lowering effects of insulin, yet it stimulates insulin secretion through the glucagon receptor (GCGR), a class B GPCR related to the incretin receptors. Glucagon essentially acts in an incretin-like fashion amplifying glucose-stimulated insulin secretion. The glucagon paracrine effect is necessary for full insulin secretion in response to glucose stimulation [20]. Pancreatic δ cells provide feedback control of neighbouring α and β cells through local circulation and the interstitial compartment. These interactions are essential for precise control and coordination of insulin and glucagon secretion. In addition to their paracrine activation by urocortin 3, δ cells receive selective inputs from multiple hormones, neurotransmitters, and nutrients, and integrate these into appropriate feedback modulation of insulin and glucagon secretion [21]. Though the contributions of α and δ cells to glucose-stimulated insulin secretion are often hard to evaluate in humans, the breakdown of these paracrine connections contributes to dysregulation of insulin- and glucagon-secretory responses in diabetes.

Insulin secretion is mainly modulated in rapid feedback with plasma glucose levels, but a long-term adaptation can also occur through changes in the number of β cells, as indicated by the progressive increase in β-cell mass occurring from birth to adulthood. Expansion of β-cell mass tends to become negligible after the age of 20–30 years [22,23], yet an increase may occur under conditions of increased insulin demand such as obesity [24,25] and pregnancy [26].

More details on the regulation of insulin secretion are available in Chapter 7, but from this brief discussion of the physiological regulation of insulin secretion, it should become apparent how abnormal insulin secretion in type 2 diabetes may arise from defective β-cell function, reduced β-cell mass, or a combination of the two.

Natural history of β-cell failure

Because of its fine regulation, assessment of insulin secretion *in vivo* requires complex methodological approaches and sophisticated modelling analysis [27,28]. Homeostasis model assessment B (HOMA-B) is a model-derived parameter reflecting β-cell function in the basal state [29]. This measure has been instrumental in describing the natural history of β-cell dysfunction in type 2 diabetes in the UK Prospective Diabetes Study (UKPDS) [30]. Individuals with type 2 diabetes already have significantly reduced β-cell function at the time of diagnosis. Moreover, β-cell function declined in an almost linear manner during the 10-year follow-up of the study, irrespective of pharmacological treatment. Because of such a linear relationship, the defect in β-cell function was extrapolated to antedate the development of hyperglycaemia by many years. The Belfast Diet Study used the same HOMA-B parameter to describe β-cell dysfunction [31]; individuals who eventually developed diabetes

already had an intrinsic 40–60% reduction in β-cell function at the outset, while over time two phases were identified:

- Phase A, which precedes overt diabetes and is characterized by a slow, constant decline of β-cell function (~2% per year).
- Phase B, characterized by a much faster decline (~18% per year), more commonly occurring with the development of diabetes.

This view is of interest because it reflects three conditions that, in recent years, have received growing experimental support: (i) genetic predisposition; (ii) early β-cell dysfunction; and (iii) factors that accelerate the rate of loss of β-cell function.

Genetic predisposition

More light has been shed in recent years on the genetic predisposition to type 2 diabetes (Chapter 12; Figure 16.3). Early linkage and candidate gene analyses and, more recently, genome-wide association studies (GWAS) have identified many genetic variants associated with increased risk of developing type 2 diabetes, although most have limited size effects that seldom exceed 10–15% [32]. The only exception is represented by variants of the *TCF7L2* gene encoding for a transcription factor involved in the Wnt-β catenin-signalling pathway [33]. In particular, the T allele of the genotypes of the single-nucleotide polymorphism (SNP) rs7903146 confers a greater risk of developing type 2 diabetes in all populations so far evaluated [33], except for the Pima [34]. More interestingly, the same genotype is associated with impaired *in vivo* [34,35] and *ex vivo* [35] insulin secretion. The *TCF7L2* genetic variants may exert both direct and indirect effects on the β cell. Thus, the increased *TCF7L2* expression found in human pancreatic islets carrying the risk allele T was inversely correlated with glucose-stimulated insulin release [35]. Moreover, people carrying the risk alleles have impaired potentiation of insulin secretion in response to GLP-1 infusion [36]. In summary, the *TCF7L2* genetic variants may be associated with reduced insulin secretion in response to both glucose and incretin hormones. Other studies have reported reduced expression of the *TCF7L2* gene in type 2 diabetes pancreatic islets along with impaired insulin secretion and β-cell survival [37].

A reduced early insulin response to both oral and intravenous glucose and greater susceptibility to diabetes have been reported for carriers of the single-nucleotide polymorphism (SNP) rs10830963 in the melatonin receptor gene (*MTNR1B*) [38,39]. These individuals have increased melatonin receptor expression in β cells, which may lead to increased melatonin binding and reduced cyclic adenosine monophosphate (cAMP)/cyclic guanosine monophosphate (cGMP) generation, accounting for impaired insulin secretion.

Other gene variants that have been associated with impaired insulin action include the G/G variants of calpain-10 gene (*CAPN10*) and *KCNJ11*. The G/G variant of SNP-43 of *CAPN10* is associated with impaired insulin response to glucose in people

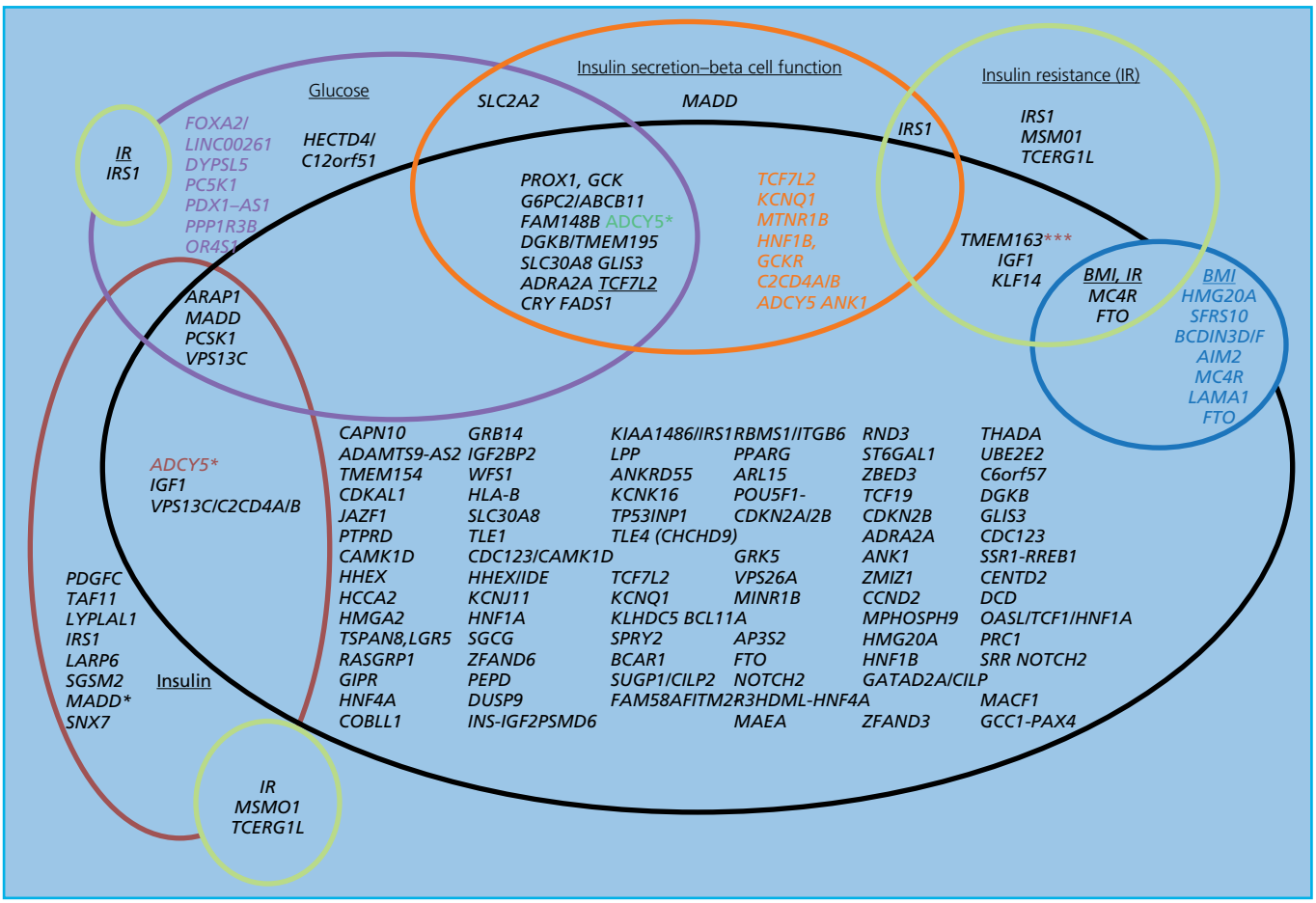

Figure 16.3 Type 2 diabetes and glycaemic trait–associated variants. The variants are represented by gene names here, which could indicate that the location is present either in the gene or in the vicinity of the gene. The white circle represents type 2 diabetes and the gene names in black in that circle represent variants only associated with type 2 diabetes. The overlapping circles indicate additional reporting associations for that variant. Source: Prasad and Groop 2015 [32]. Creative Commons Attribution License (CC BY).

without diabetes [40]. Variants of the *KCNJ11* gene may result in gain of function of the ATP-sensitive potassium channels, resulting in impaired depolarization of the β-cell membrane and altered insulin release, although such an effect becomes more apparent when the β cell is under stress conditions (i.e. glucotoxicity) [41].

Many other genes, including *HHEXZ/IDE*, *GIPR*, *PROX1*, *DGKB*, *CDKAL1*, *SLC30A8*, *CGK*, and *CDKN2A/2B*, have been associated with abnormal insulin secretion [42–59]. It is of interest that the majority of the gene variants so far associated with type 2 diabetes exert their main effect on insulin secretion, which worsens significantly with an increase in the two-hour plasma glucose level, even in people with normal glucose tolerance (i.e. two-hour plasma glucose <140 mg/dl; 7.8 mmol/l) [60,61]. In both lean individuals and those with obesity and two-hour plasma glucose levels of 120–140 mg/dl (6.7–7.8 mmol/l), β-cell function is already reduced by 60% compared with those with a two-hour plasma glucose level of<100 mg/dl (5.6 mmol/l) (Figure 16.4) [61]. The abnormalities of β-cell function become fully apparent when the insulin-secretion rate is plotted against prevalent plasma glucose levels [61,62]. This analysis clearly shows how β cells of people with a predisposition to diabetes secrete less insulin than healthy individuals for the same glucose stimulus [62]. This abnormality is often referred to as impaired glucose sensitivity [63] and it is better defined when mathematical modelling approaches are applied [64].

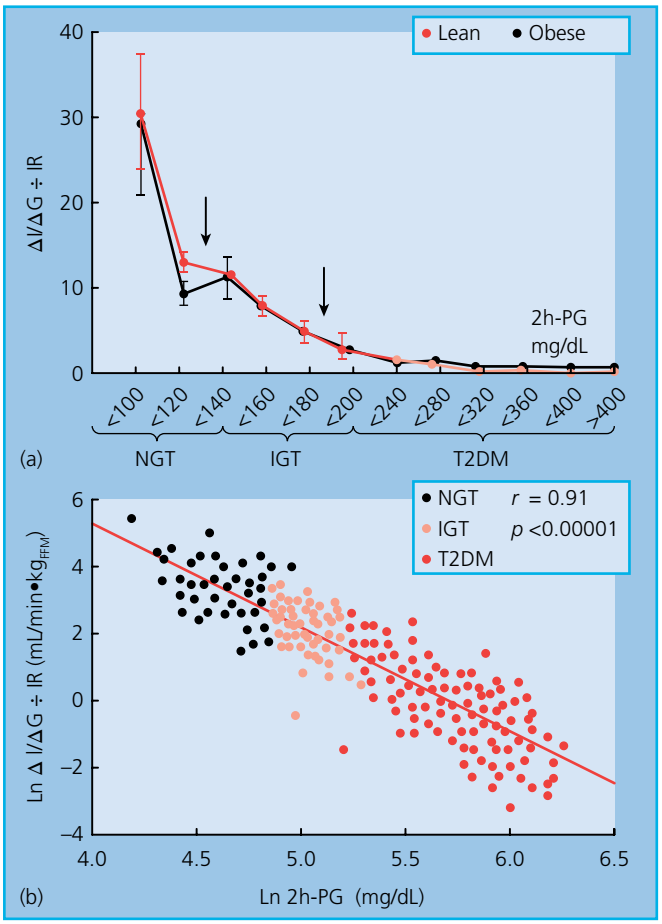

Figure 16.4 Relationship between the insulin secretion/insulin resistance index (ΔI/ΔG factored by the severity of insulin resistance measured with the euglycaemic insulin clamp) and (a) the fasting plasma glucose (FPG) and (b) the two-hour plasma glucose (two-hour PG) concentration (log–log scale). IGT, impaired glycose tolerance; NGT, normal glucose tolerance; T2DM, type 2 diabetes. Source: Gastaldelli et al. 2004 [61], Figure 12.4. Reproduced with permission of Springer.

Early β-cell dysfunction

Loss of first-phase insulin secretion is an early feature of β-cell dysfunction. Individuals with isolated impaired fasting glucose show a decrease in first-phase insulin-secretory response to intravenous glucose and early-phase insulin response to oral glucose [65]. The late-phase insulin response after an oral glucose tolerance test is less severely impaired than in people with impaired glucose tolerance who have severe defects in both early- and late-phase insulin responses. First-phase insulin secretion plays an important role in priming the liver to inhibit endogenous glucose production in response to glucose or nutrient ingestion [66,67]. Therefore, the defect in early-phase insulin secretion in impaired fasting glucose and impaired glucose tolerance results in inadequate suppression of hepatic glucose production and contributes to an excessive early rise in plasma glucose in response to an oral glucose load. In people with impaired glucose tolerance, the combination of deficient second-phase (late-phase during oral glucose tolerance test) insulin secretion and peripheral insulin resistance translates into less efficient glucose disposal. As a result, after the ingestion of a glucose load, plasma glucose concentration will continue to increase after the initial 60 minutes to remain elevated after 120 minutes. The loss of first-phase insulin not only contributes to impaired hepatic glucose metabolism [68], but also is an independent predictor of the development of type 2 diabetes [69,70].

In summary, the natural course of β-cell function suggests that the acute insulin response and glucose sensitivity play a major role in determining glucose tolerance [71]. Longitudinal studies of the Pima relating changes in insulin sensitivity and acute insulin response have clearly demonstrated that it is the worsening of the latter rather than the development of insulin resistance that marks the progression from normal glucose tolerance to impaired glucose tolerance and, eventually, type 2 diabetes [72].

The extent to which these functional abnormalities are also linked to loss of β-cell mass is still a matter of discussion [73], but β cells can undergo various changes, a phenomenon known as β-cell plasticity [74]. Recent evidence has shown how in people with pre-diabetes, under the increased demand imposed by insulin resistance, islets and exocrine cells become extraordinarily plastic [75]. Although an increased β-cell workload is a risk factor for hyperglycaemia, in most individuals there is an adaptive increase in insulin and proinsulin secretion with no apparent β-cell failure [76]. Rather, insulin resistance in these individuals induces an increase in the β-cell area, as observed in pancreas samples obtained from people without diabetes [77]. Neogenesis from duct cells and/or trans-differentiation from α cells are likely explanations for the changes in β-cell mass observed in people with insulin resistance.

Assessment of β-cell mass is largely dependent on methodological approaches [78], but several reports claim that an apparent reduction in β-cell volume of up to 60% is present in individuals with pre-diabetes [24,79,80]. The decrease in β-cell mass has been traditionally attributed to an increased rate of apoptosis [24,25,78,81,82] and, to a lesser extent, autophagy [83]. An increase in β-cell death occurs without a compensatory increase in β-cell replication owing, at least in part, to the limited regenerative capacity of adult human β cells [22,84]. Along with these mechanisms, β-cell dedifferentiation, rather than cell death, accounts for the loss of β cells in the pancreatic islet of individuals with diabetes [85,86]. Figure 16.5 summarizes the mechanisms involved in β-cell plasticity.

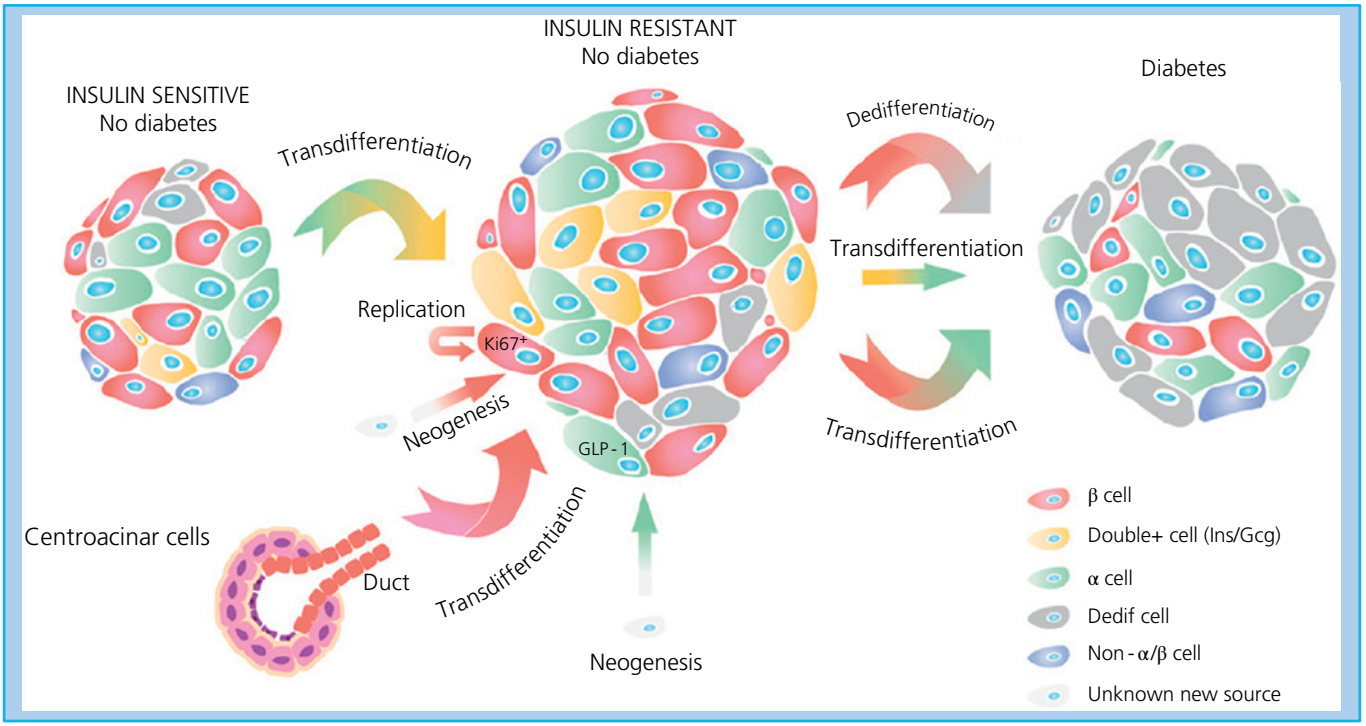

Figure 16.5 Schematic representation of the hypothetical scenario of islet plasticity. Islet plasticity is the capacity of the islet to modify its morphology and function according to different metabolic conditions. A potential explanation of the present scenario is as follows: when insulin resistance increases insulin demand, islet plasticity guarantees a twofold increase in β cells, whose origins are still debated, but some hypotheses are trans-differentiation from centroacinar and duct cells (duct red cells and centroacinar violet cells), replication (red cell Ki67+), and neogenesis from an unknown source (white to red cell); a twofold increase in the α cells trans-differentiated into insulin-producing cells (yellow double-positive cells); and a fivefold increase in the α cells via neogenesis, with a consequent increase of a potential glucagon-like peptide 1 (GLP-1) source (white to green cell). As with any compensatory mechanism, in a chronic condition it is bound to fail. The exhausted β cells undergo dedifferentiation (Dedif; a resting state, red to grey cells), the double-positive cell switches back into the original α cell (yellow cells to green cells), and the overstressed β cells trans-differentiate into α cells (red cell to green cell). Gcg, glucagon; Ins, insulin. Source: Mezza et al. [74].

Factors that accelerate the rate of loss of β-cell function; how insulin secretion progressively worsens after development of type 2 diabetes

Impaired insulin secretion and insulin-secretory capacity are the major determinants for the development of type 2 diabetes. Neither hyperglycaemia nor glucose intolerance develops in insulin-resistant individuals provided that sufficient insulin is secreted from β cells to compensate for the insulin resistance. β-cell dysfunction progresses over time and continues to worsen after diabetes has developed [30, 31]. Multiple factors contribute to the progressive loss of β-cell function and mass, the most important being the direct consequences of the altered metabolic milieu characterizing type 2 diabetes.

Hyperglycaemia

Many *in vivo* and *in vitro* studies have shown that chronic elevation of glucose concentrations impairs β-cell function (and insulin action), a phenomenon known as *glucotoxicity*. Conversely, improved glycaemic levels, both under experimental conditions and in clinical studies, have been associated with improved β-cell function [87]. The main mechanisms accounting for the negative effect of high glucose are activation of oxidative stress, the consequence of increased glucose oxidation in the mitochondria, mitochondrial dysfunction, and overproduction of reactive oxygen species (ROS) [88]. In type 2 diabetes pancreatic islets, markers of oxidative stress, are significantly increased [88] compared with normal islets and inversely related to glucose-stimulated insulin secretion. In contrast, overexpression of antioxidant factors reduces the level of markers of oxidative stress and increases β-cell responsiveness to insulin [88, 89]. The β cell is particularly susceptible to the negative effect of oxidative stress owing to an intrinsic low expression of antioxidant enzymes and reduced DNA repair capacity [90].

Increased glucose availability is also associated with activation of the glycolytic pathway in β cells and with excessive formation of fructose-6-phosphate, with subsequent increased flux through the hexosamine pathway. *in vitro* studies have clearly shown how hexosamine pathway activation interferes with the expression of genes involved in β-cell regeneration and differentiation [91] and triggers apoptosis [92].

Therefore, chronic exposure to hyperglycaemia can affect both β-cell function and mass, although such an effect is likely to be more prominent when exerted on a predisposed β cell, since in healthy individuals 72 hours of hyperglycaemia do not impair β-cell function [93].

Hyperlipidaemia

Obesity is a common condition in people with type 2 diabetes and is one of the main causes of the progressive increase in the global prevalence of the disease [94]. Obesity, and concomitant insulin resistance, are often associated with dyslipidaemia,

increased circulating leptin concentrations, and chronic inflammation [95].

Leptin receptors are expressed in β cells, and their activation directly inhibits insulin secretion [96]. Moreover, leptin inhibits insulin gene expression and affects proliferation, apoptosis, and β-cell size [96]. Expansion of adipose tissue is associated with increased cytokine release [97]; tumour necrosis factor-α and interleukin (IL)-6 affect both β-cell function and survival [98]. Moreover, apoptosis can stimulate the innate immune system with mobilization of T cells and macrophages [99]. Under stress conditions, such as those generated by excessive stimulation by glucose and free fatty acids, the concentrations of pro-inflammatory factors are increased in the pancreatic islets [100, 101] where they can trigger Fas-dependent apoptosis through activation of nuclear factor kB (NFkB). Plasma free fatty acid concentrations are commonly increased in people with type 2 diabetes and contribute to sustained insulin resistance [102] as well as impaired β-cell function [103], a phenomenon also known as *lipotoxicity*. The effects of free fatty acids on β-cell function are complex, as they are also physiological modulators of insulin secretion. Hence, under fasting conditions, an increase in plasma free fatty acids becomes essential for the maintenance of basal insulin levels and to ensure a normal insulin response to glucose [104]. Nonetheless, the toxic effect of free fatty acids can be easily demonstrated *in vitro*: even a short exposure of human pancreatic islets to an excessive free fatty acid concentration is sufficient to impair glucose-stimulated insulin release [105]. High free fatty acids levels contribute to β-cell dysfunction through intracellular accumulation of triglycerides as a response to activation of the sterol regulatory element binding proteins (SREBPs) [106], or by increased expression of uncoupling protein 2, which regulates cellular ATP production [107]. The impact on β-cell function is paralleled by a cytostatic effect due to the activation of caspase-mediated apoptosis [108]. Free fatty acids also induce the expression of nitric oxide (NO) synthase, causing marked NO overproduction. When NO production is restrained by inhibitors of inducible NO synthase, insulin secretion is significantly ameliorated [109]. NO also contributes to apoptosis through the activation of c-Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (MAPK), and Akt inhibition [110]. Elevated free fatty acid levels exert a detrimental effect on insulin gene expression as well as the expression of transcription factors that may be directly involved in the differentiation process of β cells from ductal cells [111]. Moreover, exposure of mouse islets to palmitate impairs insulin exocytosis through alteration of the tight complexes of Ca^{2+} channels with the secretory granules. Along with these mechanisms, free fatty acids activate endoplasmic reticulum stress, alter autophagy, and sustain β-cell dedifferentiation. Free fatty acids can induce endoplasmic reticulum stress through perturbations affecting endoplasmic reticulum folding capacity, leading to misfolded protein overload [112]. Excess of lipids can result in dysregulated autophagy, as indicated by an increase of autophagic vacuoles and autophagosomes, and can lower lysosomal-associated membrane protein 2 and cathepsin expression [83]. Experimental data show that challenging the β cell with free fatty acids results in a recapitulation of the typical β-cell alterations occurring in type 2 diabetes. Exposure of β cells to free fatty acids causes a depletion of forkhead box protein 1 (Foxo-1), a transcription factor responsible for the integration of nutrient- and hormone-generated signals [86]. This depletion is associated with the activation of dedifferentiation markers, suggesting that lipotoxicity may contribute to the loss of insulin-producing cells in the pancreatic islet.

In summary, like chronic hyperglycaemia, lipotoxicity can accelerate the progressive loss of β-cell function and mass. However, such an effect seems to be more apparent when the two conditions coexist, as commonly occurs in individuals with type 2 diabetes. For this reason, it may be more appropriate to refer to the combination of these effects as *glucolipotoxicity* [113]. The adverse metabolic milieu may also affect gene expression through epigenetic mechanisms. For instance, increased methylation of the PGC1-α gene promoter has been reported in pancreatic islets from cadaveric donors with type 2 diabetes; the greater the degree of methylation, the lower is the expression of the protein and the lower the glucose-stimulated insulin release [114].

Chronic β-cell stimulation

Chronic hyperglycaemia is associated with persistent β-cell stimulation and insulin biosynthesis. This process requires activation of the endoplasmic reticulum, which is responsible for the biosynthesis and folding of newly synthesized insulin (Figure 16.6) [116]. Because of glucolipotoxicity, the endoplasmic reticulum folding capacity is impaired, causing accumulation and aggregation of unfolded proteins, a condition known as endoplasmic reticulum stress [117]. Up to a certain point, this stress can be compensated via the so-called *unfolded protein response*. This adaptive and protective pathway, however, can become ineffective if endoplasmic reticulum stress is persistent and may lead to the generation of proapoptotic signals. Several studies have documented endoplasmic reticulum stress in *ex vivo* pancreatic islets of cadaveric donors with type 2 diabetes [115, 118]. In these islets, endoplasmic reticulum stress is marginally increased if they are incubated in the presence of normal glucose concentration. In contrast, exposure to higher glucose levels causes greater endoplasmic reticulum stress than in islets from cadaveric donors without diabetes (Figure 16.6) [115]. These findings suggest a greater susceptibility to proapoptotic mechanisms in the diabetic β cell. In summary, increased and persistent insulin secretion can contribute to β-cell dysfunction and survival through insulin protein misfolding in the endoplasmic reticulum.

Chronic stimulation of β cells also results in an increase in the synthesis of islet amyloid polypeptide (IAPP). This peptide is co-localized with insulin secretory granules [119] and its production parallels that of proinsulin. IAPP can form aggregates and fibrils [120], leading to the deposition of amyloid plaque that triggers an inflammatory response [121], recruitment of macrophages [122], and apoptosis [123]. The mechanism through which IAPP forms amyloid and results in β-cell damage is not completely understood. Amyloid deposition has been found in other hypersecretory conditions, such as obesity without diabetes [124] and insulinoma [125], with no apparent negative impact on β-cell function. One possible explanation for this paradox is that the negative effect of amyloid may require concomitant glucolipotoxicity. In line with this hypothesis is the observation that pancreatic islet amyloid can be found in up to 90% of people with type 2 diabetes [126] and that the degree of deposition correlates with the duration and severity of the disease [127].

Impaired incretin effect

GLP-1 and GIP are physiological factors involved in β-cell function and survival [128] and they are the main players in the incretin effect [14]. This effect is characteristically lost in type 2 diabetes,

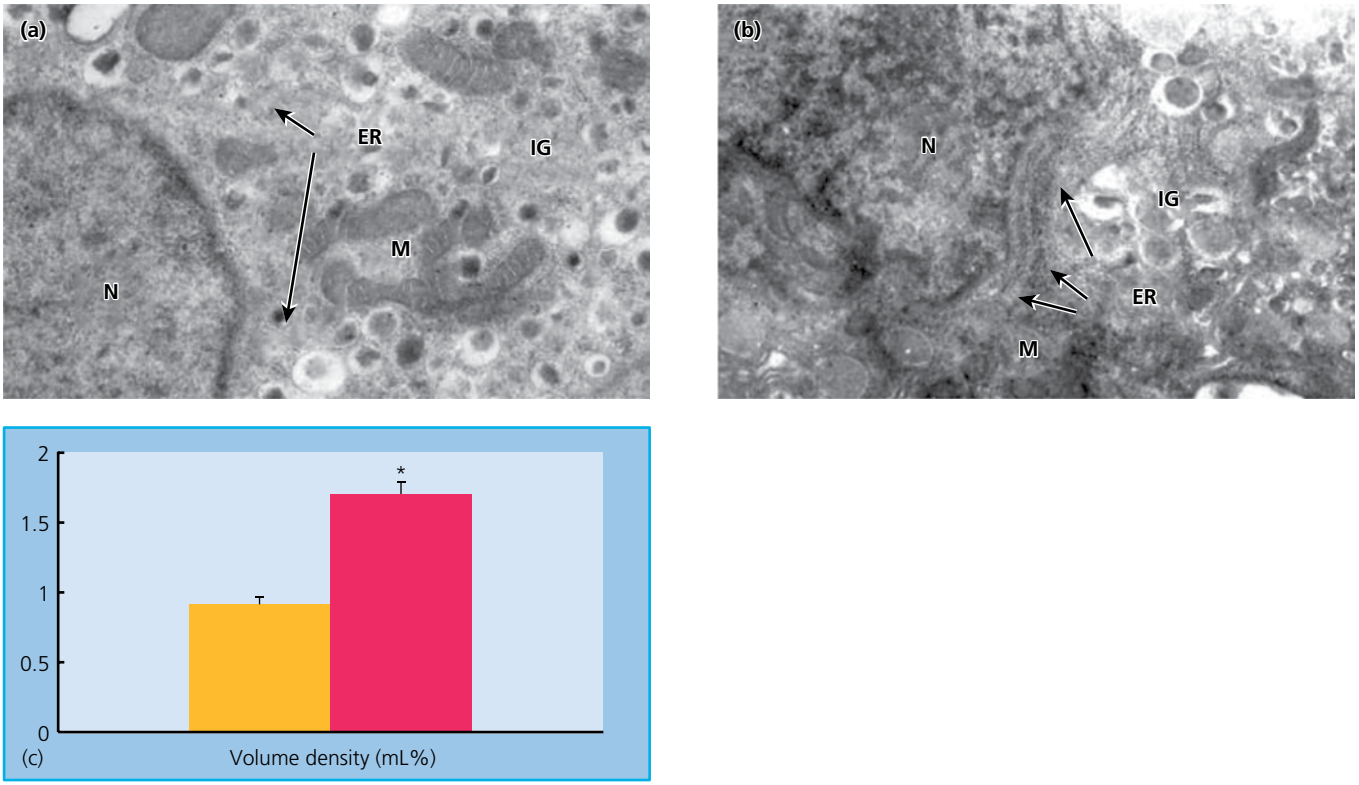

Figure 16.6 (a, b) Electron microscopy images showing the endoplasmic reticulum (ER) in (a) non-diabetic β cells and (b) type 2 diabetes β cells. The ER components (arrows) are scarcely visible in non-diabetic cells and more apparent in type 2 diabetes cells. Magnification ×10 000. IG, insulin granules; M, mitochondria; N, nucleus. (c) The ER density volume was significantly higher in type 2 diabetes β cells (red box) than non-diabetic β cells (yellow box). *$p < 0.05$ (Student's *t*-test for unpaired data). Source: Marchetti et al. 2007 [115]. Reproduced with permission of Springer.

although it is still a matter of discussion whether this alteration is a primary defect or an acquired one [129]. In both cases, the loss of the incretin effect results in poor potentiation of the insulin release in response to the ingestion of a meal and excessive post-prandial glucose excursion [130]. Whether this defect can also contribute to loss of β-cell mass is unclear, at least in humans, but pre-clinical studies have provided evidence for an effect of GLP-1 in reducing apoptosis and stimulating β-cell regeneration and differentiation in experimental murine models [131].

GLP-1 is mainly secreted by the L cells of the lower intestine, but GLP-1 can also be synthesized by the α cells of the pancreatic islet [132, 133]. These cells also express dipeptidyl peptidase 4 (DPP-4), the peptidase responsible for GLP-1 inactivation [134]. GLP-1 production is increased in pancreatic islets from cadaveric donors with type 2 diabetes [133], whereas DPP-4 activity is reduced [134]. The extent to which these mechanisms may ensure an *in vivo* increase in local GLP-1 levels is difficult to ascertain, but the increase in intra-islet GLP-1 availability could be seen as an attempt to protect the β cells [135].

Diabetes treatments

Improved glycaemic levels can relieve glucotoxicity and restore, to some extent, β-cell function [87]. However, there is discussion on the potential direct effects that currently available glucose-lowering therapies may exert on the preservation of β cells. Potential protective effects have been claimed with the use of DPP-4 inhibitors [136, 137], GLP-1 receptor agonists [138, 139], and pioglitazone [140]. GLP-1 receptor agonists protect β cells from lipotoxicity by increasing cell defences [141], reducing inflammatory response [142], and preventing autophagy inhibition [143]. Glitazones can reduce oxidative stress [144], inflammation, and endoplasmic reticulum stress [145] associated with lipotoxicity. Incubation of pancreatic islets of individuals with type 2 diabetes in the presence of therapeutic concentrations of metformin increases insulin content and the number and density of mature insulin granules, improves glucose-induced insulin release, and reduces apoptosis along with normalization of several markers of oxidative stress [146]. Weight reduction and physical activity may exert a favourable effect on β-cell function of people with type 2 diabetes. Fat accumulation has been found in intrapancreatic adipocytes of these individuals [147] and its reduction with a very low-calorie diet is associated with a recovery of first-phase insulin secretion [148]. Exercise can also elicit a decrease of pancreatic fat, but can also enhance IL-6. Administration of IL-6 or elevated IL-6 concentrations in response to exercise stimulate GLP-1 secretion from intestinal L cells and pancreatic α cells, improving insulin secretion and glycaemia in experimental animals [132].

In *ex vivo* studies, concern has been expressed with respect to the effects of sulfonylureas on the β cell. *In vitro* experiments have shown increased β-cell apoptosis [149], although some difference

may exist among different sulfonylureas. In isolated human pancreatic islets, glibenclamide but not repaglinide activates β-cell apoptosis [149]. Other observations have indicated a reduced insulin content in pancreatic islets incubated in the presence of glimepiride, glibenclamide, and chlorpropamide, although no change in insulin release in response to glucose was observed with glimepiride [150]. In cultured β-cell lines, no activation of apoptosis was found with gliclazide treatment along with some antioxidant effect noted in human pancreatic islets [151].

The real impact of these findings is still unclear. In the clinical setting, the durability of the glucose-lowering efficacy of sulfonylureas is claimed to be poorer than with other anti-diabetes agents [152]. These findings are in keeping with animal studies showing that chronic glibenclamide treatment causes loss of insulin-secretory capacity due to β-cell hyperexcitability [153]. However, the same studies also revealed rapid reversibility of this secretory failure, arguing against β-cell apoptosis or other cell death induced by sulfonylureas. In contrast, these findings support earlier observations showing *in vivo* restoration of β-cell response to sulfonylureas, once sustained sulfonylurea therapy was discontinued [154].

In summary, on the development of overt hyperglycaemia, several factors, including chronic hyperglycaemia, obesity, increased free fatty acid availability, persistent stimulation of β cells, and, potentially, the use of specific drugs, may contribute to the acceleration of the decline in insulin-secretory capacity of individuals with type 2 diabetes and progression of the disease. These accelerating factors promote common damage mechanisms, including oxidative stress, endoplasmic reticulum stress, inflammation, and immune system activation (Figure 16.7) [155]. Because of these mechanisms, a vicious cycle develops by which the ability of the β cells to cope with hyperglycaemia and insulin resistance becomes weaker and the impact of the accelerating factors becomes greater. These factors impair both the function and the survival of the β cells, although the relative contribution of the two remains to be established.

β-cell dysfunction: exhaustion or insufficient mass?

β-cell dysfunction and loss of β-cell mass both contribute to the pathogenesis of hyperglycaemia in type 2 diabetes. At the time of diagnosis of type 2 diabetes, the β-cell mass is already reduced by 30–40% [24, 79–81]. This loss of insulin-producing cells has been traditionally viewed as the result of the activation of apoptosis and other cell-death mechanisms. More recently it has been appreciated that metabolic stressors can induce dedifferentiation and/or trans-differentiation. Through dedifferentiation mature β cells can revert to a more progenitor-like stage and lose insulin-secretory capacity. This phenomenon has been extensively documented in experimental models of insulin resistance [156] and also reported in a study in individuals with type 2 diabetes [157]. Under similar metabolic stressful conditions, the β cell can also convert to different hormone-expressing cells, as shown by genetic lineage-tracing analysis carried out in experimental models [158]. Such an accurate analysis is not feasible in humans, yet the finding that these cells may spontaneously trans-differentiate in ductal cells has generated interest in therapeutic reprogramming in diabetes [159].

Whatever the mechanisms involved, the decreased number of cells is unlikely to account for the distinctive defect in insulin secretion that characterizes type 2 diabetes even before the time of diagnosis. Experimental data have shown that, at least in rodents, no disturbances in glucose homeostasis arise provided that the β-cell mass remains >20% [160]. In humans, diabetes

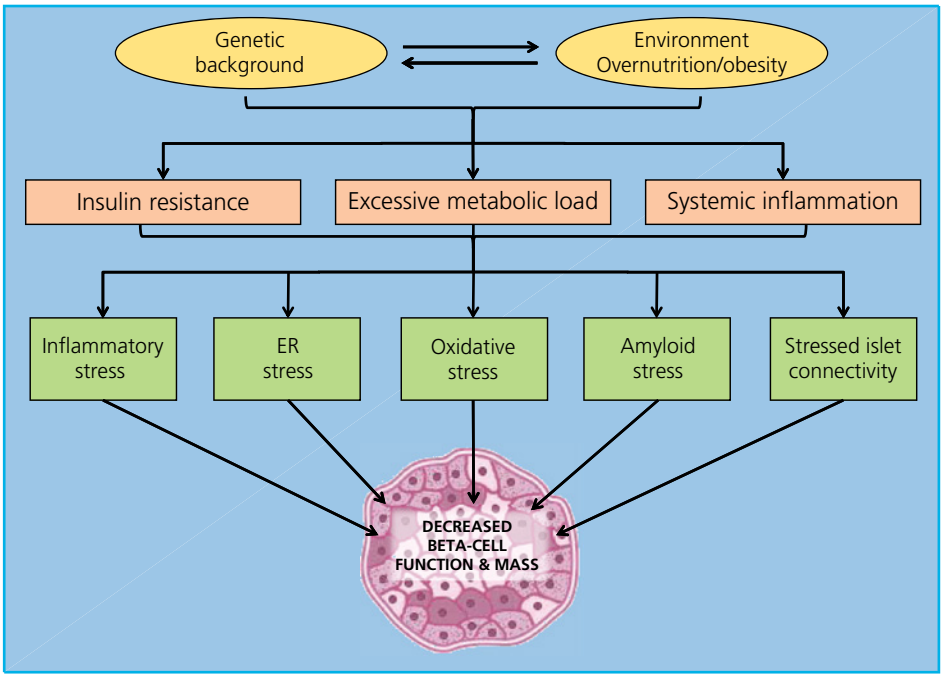

Figure 16.7 Mechanisms of β-cell damage in type 2 diabetes. Environmental factors and genetic backgrounds interact to activate stress processes that contribute to functional abnormalities and also progressive loss/dedifferentiation of β cells. ER, endoplasmic reticulum. Source: Adapted from Halban et al. 2014 [155].

develops when the β-cell area declines by ~65% [161]. The suggestion that the reduction in β-cell mass may not be sufficient *per se* to result in glucose intolerance is supported by the simple observation that a large overlap exists between the β-cell mass of individuals with and without diabetes (Figure 16.8) [162]. Moreover, hemi-pancreatectomy performed in normal individuals for the purpose of pancreas donation is not followed by major disturbances in insulin secretion [163]. The β-cell mass may also be a misleading measurement as one may argue whether it is the number of β cells (or cell area) or the insulin content per cell (and therefore the total insulin content in the pancreas) that is of importance. Relevant to this issue is the finding that the β-cell mass declines with the duration of the disease, although the insulin content per cell tends to increase [162]. The progressive loss of β cells in diabetes is likely to be the consequence of even a mild elevation of plasma glucose levels and concomitant increased secretory demand sustained by insulin resistance, particularly if these mechanisms operate on a genetically predisposed β cell. Consistent with this view are animal experiments showing how a 60% pancreatectomy in dogs does not result in an alteration of insulin secretion unless the plasma glucose levels are modestly increased by intravenous glucose infusion [163]. These results are also in keeping with the few available human studies. In people without diabetes, scheduled for pancreaticoduodenectomy surgery, despite comparable functional mass and fasting glucose and insulin levels at baseline, only pre-existing defects in β-cell function (reduced first-phase insulin secretion and glucose sensitivity) predicted the risk of developing hyperglycaemia after partial pancreatectomy (Figure 16.9), a model of acute β-cell mass reduction, suggesting that these functional alterations could be pivotal to the pathogenesis of type 2 diabetes [77].

This observation does not imply that loss of β-cell mass is less important than β-cell function. In fact, reduction of β-cell mass is the trigger that reveals the pivotal role of first-phase insulin secretion in predicting the appearance of impaired glucose metabolism after partial pancreatectomy [164]. Moreover, in healthy people with no family history of diabetes, a 72-hour glucose infusion resulting in constant elevation of post-absorptive plasma glucose levels just above 110 mg/dl (6.1 mmol/l) was associated with a potentiation of both first- and second-phase insulin secretion rather than an impairment [93]. In contrast, when normo-tolerant first-degree relatives of individuals with type 2 diabetes were infused with fat emulsions to increase circulating free fatty acid levels, a marked impairment of insulin secretion became apparent [165] (Figure 16.10).

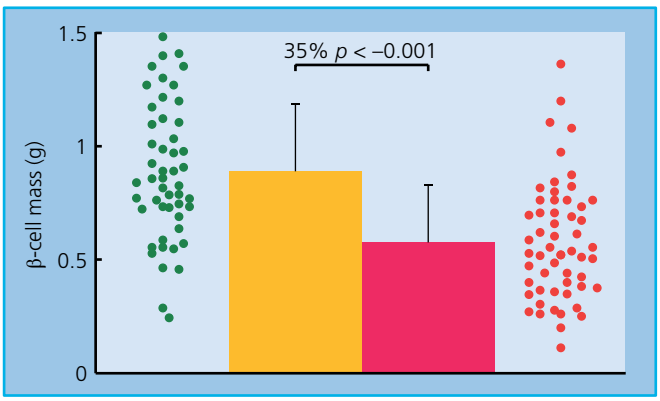

Figure 16.8 β-cell mass in the pancreas of people without (left) and with type 2 diabetes (right). Data are presented for individual values as scatterplots and mean values ±SD (standard deviation) as columns. Although on average the β-cell mass is about 40% less in people with type 2 diabetes, there is some degree of overlap between the two groups. Source: Rahier et al. 2008 [162]. Reproduced with permission of John Wiley & Sons.

Such a rapid worsening of insulin secretion is unlikely to be due to a sudden reduction in the number of β cells; rather, this is much more congruent with a further impairment of the mechanisms responsible for glucose sensing and insulin response. Finally, the results of bariatric surgery in people with diabetes provide stronger support for the primacy of impaired β-cell function rather than loss of β cells. Even in individuals with type 2 diabetes with long-standing duration of the disease, the surgical procedure is followed by an almost immediate improvement of β-cell function associated with simplification, if not withdrawal, of pharmacological glucose-lowering therapy [166–168]. β-cell dysfunction may also be the result of the loss of islet organization. As mentioned, insulin secretion is pulsatile in nature, with a slow ultradian periodicity (<140 minutes) and a high-frequency periodicity [169]. These oscillations require sophisticated coordination of the secretory activity of the individual β cells dispersed through the ~1 million pancreatic islets present across the pancreatic tissue. Such connectivity recognizes several mechanisms operating in concert, including neural circuits, gap junctions, activity of primary cilia, and paracrine signalling [55]. Recently it has been suggested that, along with genomic imprinting [170], lipotoxicity may disrupt the incretin effect on this connectivity [171], possibly through downregulation of connexin 36, a component of gap junctions [172].

A further element that could contribute to impaired β-cell function has been recently identified in the functional heterogeneity of insulin-producing cells within a single islet. Recent data have indicated the existence of β cells that differ one from another by morphology, distribution, function, connectivity, and gene expression profile [173]. This heterogeneity refers also to islet electrical excitability and connectivity, which is altered early in the natural history of diabetes [174].

In conclusion, the available evidence indicates the existence of multiple abnormalities accounting for β-cell dysfunction in type 2 diabetes that seem affect primarily function more than β-cell mass. The recent appreciation that β-cell dedifferentiation and/or trans-differentiation rather than apoptosis may account for reduced functional β-cell mass [175] speaks against the old concept of β-cell exhaustion and opens to the possibility of recovering proper insulin secretion through reprogramming. This views also fits with the observation that β-cell dedifferentiation enhances degranulation [176] and that experimental insulin granules can be restored through a decrease in blood glucose [177] and insulin secretion recovered even in islets from individuals with type 2 diabetes [178].

Conclusion

β-cell dysfunction is an early feature in the natural course of type 2 diabetes and plays a critical role in the development of glucose intolerance and progression of the disease. This distinctive

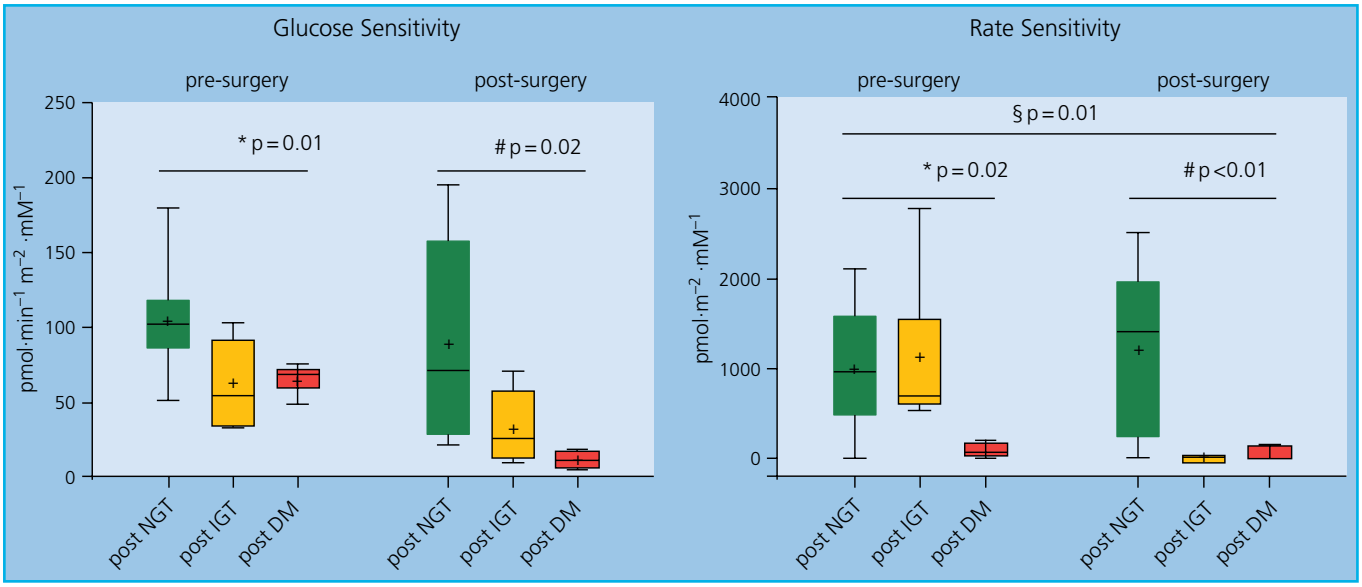

Figure 16.9 Oral glucose tolerance (OGTT)-derived glucose sensitivity (a) and rate sensitivity (b), i.e. measures of β-cell function, before and after partial pancreatectomy, categorized on the basis of glucose tolerance after surgery: normal glucose tolerance (NGT, green box); impaired glucose tolerance (IGT, orange box); and diabetes (DM, red box). The relationship between variables was derived by linear regression analysis. Variables were regressed against glucose tolerance status by using (a) pre-pancreatectomy values and (b) post-pancreatectomy values adjusted for pre-pancreatectomy values. *p < 0.05 before surgery; #p < 0.05 after surgery; §p < 0.05 before surgery adjusted for after surgery. Box plots indicate median and interquartile range; whiskers indicate 2.5th to 97.5th percentile ± mean value. Source: Mezza et al. 2021 [77].

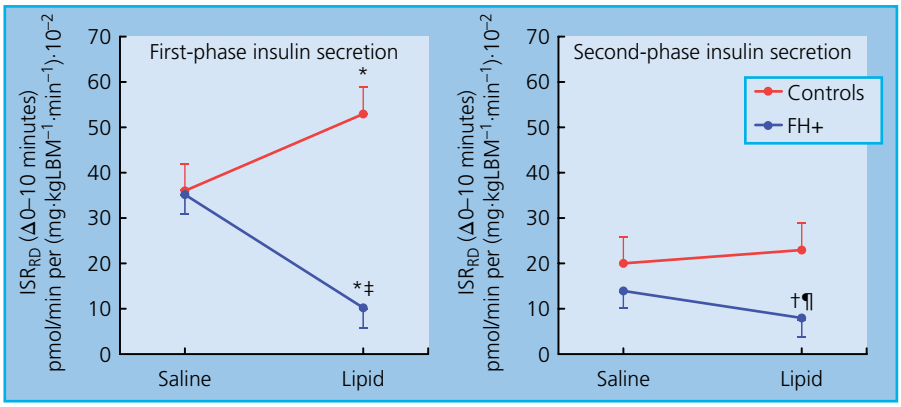

Figure 16.10 Insulin secretion rates (ISRs) during hyperglycaemic clamp studies related to the prevailing severity of insulin resistance (ISR_{Rd}). On comparing control participants with healthy participants with a strong family history of type 2 diabetes (FH_+), the first-phase ISR_{Rd} is similar during the saline studies; with lipid infusion, the first-phase ISR_{Rd} deteriorates in FH_+ participants, whereas it increases in control participants. The second-phase ISR_{Rd} is also reduced by lipid infusion in the FH_+ group but is unchanged in healthy controsl. *p < 0.01 vs saline; †p < 0.05 vs saline; ‡p < 0.001 vs control participants; ¶p < 0.05 vs control participants. Source: Adapted from Kashyap et al. 2003 [165].

alteration recognizes a genetic background, with several genetic variants specifically associated with impaired β-cell function and survival. In people predisposed to diabetes and in those with prediabetes, both a reduction in β-cell mass and, to a greater extent, impaired insulin secretion are fully apparent. A minimal increase in fasting plasma glucose levels is already accompanied by a typical loss of first-phase insulin secretion. Obesity, development of hyperglycaemia and dyslipidaemia (in particular increased plasma free fatty acid concentrations), and chronic overstimulation of insulin secretion can activate pathogenic mechanisms (glucolipotoxicity, oxidative stress, inflammation, endoplasmic reticulum stress, epigenetic modifications, amyloid deposition) that can accelerate the progression of β-cell impairment. The same mechanisms activate apoptosis, dedifferentiation, and possibly trans-differentiation, and alter autophagy. Concomitant insufficient β-cell regeneration or differentiation results in a reduction of functional β-cell mass. This process is a progressive, though potentially reversible, process. Therefore, preservation of β-cell function is key to preventing deterioration of glucose tolerance and development of diabetes. Moreover, tight control of the accelerating factors may slow the progression of the disease and result in more durable glycaemic levels over the years.

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17 Insulin Resistance in Type 2 Diabetes

Michael Roden[1,2,3], Kitt Falk Petersen[4,6], and Gerald I. Shulman[4,5,6]

[1] Department of Endocrinology and Diabetology, Medical Faculty and University Hospital, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany

[2] Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich-Heine University Düsseldorf, Düsseldorf, Germany

[3] German Center for Diabetes Research, Partner Düsseldorf, München-Neuherberg, Germany

[4] Department of Internal Medicine, Yale School of Medicine, New Haven, CT, USA

[5] Department of Cellular & Molecular Physiology, Yale School of Medicine, New Haven, CT, USA

[6] Yale Diabetes Research Center, New Haven, CT, USA

Key points

- Insulin resistance is a major factor in the pathogenesis of type 2 diabetes, but it can be also observed in type 1 diabetes.
- Impaired insulin-stimulated muscle glycogen synthesis, due to defects in glucose transport, is the key contributor to whole-body insulin resistance.
- Ectopic fat storage leads to increases in plasma membrane *sn*-1,2-diacylglycerol content, which in turn activates novel protein kinase Cε in muscle, liver, and adipose tissue, leading to phosphorylation of the insulin receptor on threonine^{1160}, causing inhibition of insulin receptor kinase activity and insulin resistance.
- Reduced mitochondrial function is a predisposing factor for ectopic lipid deposition, increased plasma membrane *sn*-1,2-diacylglycerol content, and insulin resistance.
- Macrophage-induced adipose tissue lipolysis promotes increased hepatic gluconeogenesis, hepatic insulin resistance, and fasting hyperglycaemia in suboptimally managed diabetes by increasing hepatic acetyl-coenzyme A content, which in turn activates pyruvate carboxylase activity and increased glycerol conversion to glucose.

Definition and measurement of insulin resistance in humans

The sensitivity to insulin results from its biological effects in the insulin-responsive tissues, predominantly skeletal muscle, liver, and adipose tissue. Impaired insulin sensitivity, also termed insulin resistance, is generally defined as reduced glucose clearance in skeletal muscle, impaired suppression of glucose production by the liver, and decreased rates of lipolysis in adipose tissue or by decreased combined action on whole-body glucose disposal (Figures 17.1 and 17.2).

In 1936, Himsworth [3] provided the first protocol for the standardized *in vivo* determination of insulin sensitivity from the glycaemic response on intravenous insulin application. Decades later, the hyperinsulinaemic–euglycaemic clamp test [4–6] became the gold standard for measuring whole-body insulin sensitivity *in vivo* and for identifying insulin-resistant people [7,8]. This steady-state method relies on constant insulin and glucose concentrations, which disrupt the physiological feedback loop between blood glucose concentrations and insulin secretion. The glucose infusion rates required to maintain a defined level of glycaemia will then reflect whole-body insulin sensitivity, given as the *M*-value [5]. Combined with other techniques, including indirect calorimetry, isotopic tracer dilution, and nuclear magnetic resonance (NMR) spectroscopy of muscle, liver, and brain, the clamp allows the assessment of oxidative and non-oxidative glucose metabolism, systemic, and even tissue-specific fluxes of glucose and other metabolites under *in vivo* conditions. In contrast to the steady-state clamp test, other techniques such as the intravenous [9] or oral [10] glucose tolerance tests [7,8] describe parameters of insulin action, such as the S_i or oral glucose insulin sensitivity (OGIS) values, from modelling of the dynamic changes of plasma glucose and insulin concentrations over time. These tests can also provide measures of insulin secretion and kinetics during the same experiment.

As these techniques are time consuming and laborious and require experienced personnel, simpler tests have been developed for assessing insulin sensitivity in epidemiological studies. The commonest indices, homeostasis model assessment (HOMA-IR, HOMA-B) [11] and QUICKI [12], are calculated from fasting plasma glucose and insulin or C-peptide concentrations [13]. The general limitation of this approach results from the fact that the liver is responsible for providing fasting plasma glucose [14]. Under these conditions, 60% of glucose is utilized in non-insulin-dependent tissues, such as the brain, and to a lesser extent in insulin-sensitive tissues, such as muscle and liver [15]. The insulin resistance indices obtained during fasting therefore do not correlate closely with clamp-derived glucose disposal [16,17]. Finally, these

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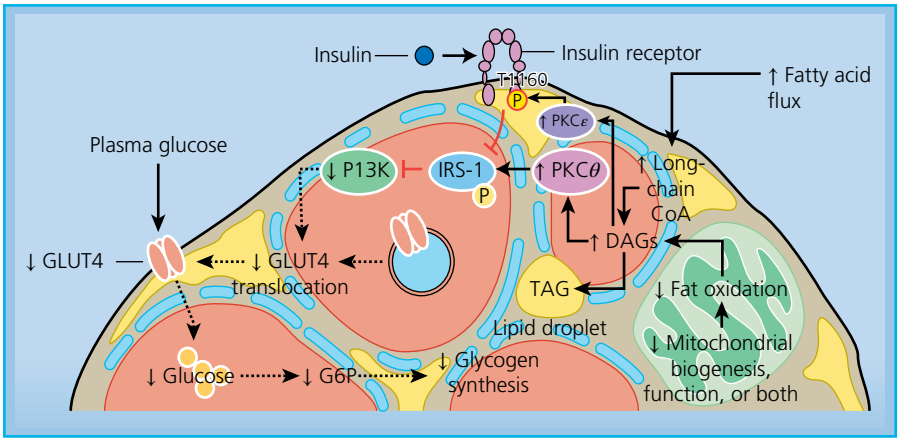

Figure 17.1 Cellular mechanism of insulin resistance in human skeletal muscle. Augmented lipid availability, mainly increased fatty acid flux, raises the intramyocellular pool of the long-chain fatty acyl (CoA) pool, which fuels mitochondrial oxidation or serves to synthesize diacylglycerols (DAGs) for storage as triglyceride (TAG) lipid droplets. When fatty acid delivery and uptake exceed the rates of mitochondrial long-chain fatty acyl-CoA oxidation and incorporation of DAGs into TAGs, the intramyocellular DAG content transiently or chronically increases. Specifically, increases in plasma membrane *sn*-1,2-DAGs lead to activation of novel protein kinase C (nPKC) isoforms (PKCε and PKCθ). Translocation of the PKCε to the membrane leads to phosphorylation of the insulin receptor on threonine^{1160} (T1160), leading to inhibition of insulin receptor kinase (IRK) activity, whereas activation of PKCθ leads to increased serine phosphorylation of insulin receptor substrate 1 (IRS-1) on critical sites (e.g. Ser^{1101}), which in turn blocks insulin-stimulated tyrosine phosphorylation of IRS-1 and the binding and activation of phosphatidylinositol 3-kinase (PI3K). Both of these events result in reduced insulin-stimulated recruitment of glucose transporter type 4 (GLUT4) units to the membrane, leading to impaired insulin-stimulated glucose uptake and phosphorylation to glucose-6-phosphate and ultimately decreased insulin-stimulated glycogen synthesis. Source: Shulman 2014 [1]. Copyright © 2014 Massachusetts Medical Society. Reprinted with permission.

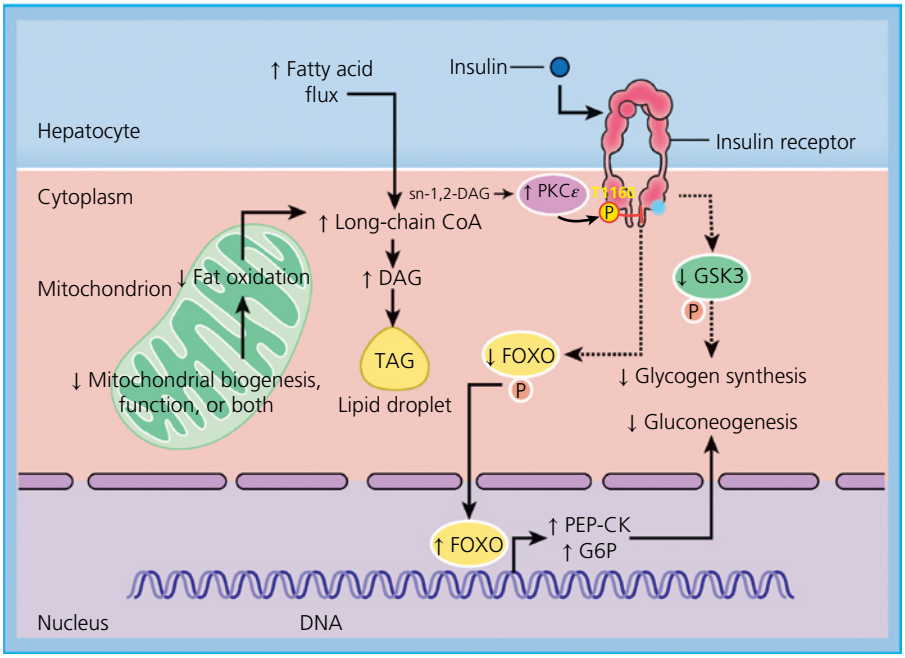

Figure 17.2 Cellular mechanism of insulin resistance in the human liver. An imbalance of intrahepatocellular fluxes gives rise to increases in plasma membrane *sn*-1,2-diacylglyerols (*sn*-1,2-DAGs), when DAG synthesis, from both fatty acid re-esterification and *de novo* lipogenesis, exceeds the rates of mitochondrial oxidation of long-chain fatty acyl-coenzyme A (CoA) and/or the rates of *sn*-1,2-DAG incorporation into triglycerides (TAGs) and lipid droplets. Increases in plasma membrane *sn*-1,2-DAGs leads to translocation and activation of protein kinase Cε (PKCε) to the plasma membrane, where it binds to the insulin receptor and phosphorylates it on threonine^{1160} (threonine^{1150} in mice), which in turn leads to inhibition of IRK activity and downstream insulin signalling events. In turn, phosphorylation of glycogen synthase kinase 3 (GSK3) increases, while that of forkhead box subgroup O (FOXO) decreases. This results in inhibition of glycogen synthase activity and thereby lowering insulin-stimulated glycogen storage, and in FOXO-mediated gene transcription of the gluconeogenic enzymes (e.g. phosphoenolpyruvate carboxykinase [PEP-CK] and glucose-6-phosphate), with decreased insulin suppression of hepatic gluconeogenesis. It is also important to note that untargeted phosphoproteomic studies have identified many other proteins that are phosphorylated by activation of PKCε besides the insulin receptor, such as p70S6K, which will also cause insulin resistance downstream of the insulin receptor [2]. Source: Shulman 2014 [1]. Copyright © 2014 Massachusetts Medical Society. Reprinted with permission.

indices can be used for describing insulin sensitivity in recent-onset diabetes [18], but may not be valid in long-standing diabetes when the physiological relationship between circulating glucose and insulin or C-peptide is disrupted.

Insulin resistance as a risk factor for type 2 diabetes

Insulin resistance may occur independently of inadequate insulin secretion and be a prerequisite for incident type 2 diabetes [19–22]. The direct evidence for a time-dependent association between insulin sensitivity and deterioration of glucose tolerance preceding type 2 diabetes comes from comparison of population trajectories of fasting and post-glucose challenge plasma glucose concentrations with HOMA-S and insulin secretion (HOMA-B) in people developing or remaining free of diabetes in the longitudinal Whitehall II study [23]. This study found that individuals had 29% lower HOMA-S but 13% greater HOMA-B values at 13 years before the onset of diabetes. HOMA-S decreased linearly until about five years before diagnosis and with an even steeper slope during the last five years prior to diagnosis. Thus, insulin resistance represents an early abnormality, which is compensated by augmented β-cell function for a long time before the insulin–glucose feedback loop fails. Insulin resistance not only predicts type 2 diabetes, but also correlates with cardiovascular disease and outcomes [24,25].

The most important factors predicting type 2 diabetes are male sex, increasing age, overweight, and obesity [26]. Insulin resistance is frequent in people with the so-called metabolic syndrome, which, in addition to visceral obesity, comprises dyslipidaemia, hypertension, and dysglycaemia. Hyperuricaemia, arteriosclerosis, microalbuminuria, platelet hyperaggregation, and antifibrinolysis, sleep apnoea, and male hypogonadism have also been associated with this syndrome. The risk of type 2 diabetes is also markedly higher in first-degree relatives of individuals with type 2 diabetes and in women with a history of gestational diabetes mellitus or polycystic ovary syndrome, all of whom are mostly insulin resistant [16,17, 27–30]. These associations raise the question of whether chronic insulin resistance represents an inherited or an acquired abnormality. Despite the fact that a family history of type 2 diabetes raises the risk of type 2 diabetes in relatives, even the combination of all currently known genes associated with diabetes adds little to the prediction of type 2 diabetes based on sex, age, and body mass index [26]. Marked differences exist at the clinical onset of diabetes: clustering based on five variables including HOMA-IR identified, aside from autoimmune diabetes, four endotypes of type 2 diabetes, with one characterized by severe insulin resistance [18,30]. At diagnosis, this endotype also shows the most pronounced liver steatosis and low-grade inflammation, whereas the other endotypes exhibit increasing insulin resistance over the next five years [18].

Dietary and physical activity interventions that improve insulin resistance markedly reduce the incidence of type 2 diabetes [31], underscoring the predominant role of lifestyle in both the pathogenesis of insulin resistance and the progression of type 2 diabetes. Several metabolic factors related to lifestyle associate with or predict insulin resistance and type 2 diabetes. These factors are mainly related to lipid metabolism, such as plasma concentration of non-esterified fatty acids [32], serum triacylglyceride-to-serum high-density lipoprotein (TAG/HDL-C) [33,34], and ectopic fat content in skeletal muscle (intramyocellular triacylglycerols [TAGs]) [35–37] or in the liver (hepatocellular lipid content) [38,39]. In addition, red meat intake was among the best predictors of type 2 diabetes in a large epidemiological study [40] and plasma concentrations of amino acids also predict type 2 diabetes [41].

Altered secretion patterns of cytokines, mainly derived from adipose tissue, and elevation of circulating pro-inflammatory markers such as C-reactive protein may predict insulin resistance and type 2 diabetes [42,43]. Adiponectin is the only anti-inflammatory cytokine with lower circulating levels before the onset of type 2 diabetes [44], while concentrations of others, such as interleukin-1 receptor antagonist (IL-1RA), transforming growth factor β1 (TGF-β1) and growth differentiation factor-15 (GDF-15) are increased [45] and indicate the presence of a compensatory, but eventually futile, counter-regulation of pro-inflammatory stimuli. Although all metabolic and inflammation-related variables circulate systemically and may cause effects in several tissues simultaneously, insulin resistance may sequentially affect certain insulin-responsive tissues, such as skeletal muscle, liver, and adipose tissue.

Insulin resistance in skeletal muscle

^{13}C-NMR spectroscopy permitted for the first time non-invasive, direct assessment of rates of insulin-stimulated muscle glycogen synthesis *in vivo*. Using this approach, it was found that muscle glycogen synthesis accounts for ~90% of insulin-stimulated whole-body glucose disposal and for virtually all the non-oxidative glucose disposal in healthy insulin-sensitive humans [46]. People with type 2 diabetes exhibit a 60% reduction in insulin-stimulated muscle glycogen synthesis, which represents the main abnormality underlying their insulin resistance [46,47]. Similarly, after the ingestion of mixed meals, the increase in muscle glycogen synthesis was ~30% lower in people with type 2 diabetes despite doubled serum insulin concentrations compared with insulin-sensitive individuals [48,49]. Applying combined ^{13}C/^{31}P NMR spectroscopy to directly measure the time course of intracellular concentrations of key metabolites in the pathway of muscle glycogen synthesis (intramyocellular glucose, glucose-6-phosphate, and glycogen) revealed diminished increases in glucose-6-phosphate [50] and intramyocellular glucose concentrations [47] in skeletal muscle of type 2 diabetes during hyperinsulinaemia (Figure 17.1). This indicates that an abnormality in insulin-stimulated glucose transport via glucose transporter 4 (GLUT4) is the main abnormality responsible for muscle insulin resistance in people with type 2 diabetes and/or obesity and in insulin-resistant first-degree relatives of people with type 2 diabetes [51]. Further studies to delineate the mechanism by which insulin resistance affects recruitment of GLUT4 have indicated that upstream defects in the insulin signalling cascade are responsible for the impaired GLUT4 translocation [1,52].

It has been suggested previously that hyperglycaemia may cause these abnormalities by a mechanism summarized as *glucose toxicity* [53,54], which seems to be supported by similar impairments of insulin-stimulated glycogen synthesis and glucose-6-phosphate increases in skeletal muscle in individuals with suboptimally managed type 1 diabetes [55,56]. However, since insulin-resistant but normoglycaemic humans, such as lean relatives of people with obesity or older people with type 2 diabetes exhibit identical effects, mechanisms other than glucose toxicity have to explain the insulin resistance in the skeletal muscle of these groups [51,57–59].

Most insulin-resistant but normoglycaemic humans feature dyslipidaemia with elevated very low-density lipoproteins (VLDLs), TAGs, and/or fatty acids, which also predict not only type 2 diabetes [32,60–62] but also cardiovascular mortality [63]. Excess lipid storage in the form of obesity has long been associated with insulin resistance, but ^{1}H-NMR studies provided evidence for an even stronger relationship between intramuscular [64] and intramyocellular TAG content and muscle insulin resistance than for body fat content [37,64–66]. Intramyocellular TAG concentrations can be measured non-invasively by ^{1}H NMR spectroscopy and increased concentrations have been termed ectopic lipid accumulation or metabolic obesity. The observation of augmented ectopic lipid deposition in insulin-resistant states infers that intracellular TAGs or lipid metabolites could mediate the effect of circulating lipids on insulin action (Figure 17.1). From early pre-clinical studies, Randle explained the impaired glucose metabolism in type 2 diabetes by an interaction with fatty acids, termed the *glucose–fatty acid cycle* [67]. This hypothesis postulated that fatty acid oxidation first raises the mitochondrial concentration ratio of acetyl-coenzyme A (acetyl-CoA)/CoA, which would inhibit the pyruvate dehydrogenase (PDH) complex. The subsequent rise in citrate would inhibit phosphofructokinase-1 and raise glucose-6-phosphate, which would then inhibit hexokinase and finally increase intracellular glucose concentrations and reduce muscle glucose uptake. In contrast, short-term elevations of plasma TAGs and fatty acids resulted in marked muscle insulin resistance, but a blunted rise in intramyocellular glucose and glucose-6-phosphate, as measured using ^{13}C/^{31}P NMR spectroscopy during insulin stimulation in healthy humans. Lipid-induced muscle insulin resistance in humans thereby results from reduction of insulin-stimulated glucose transport into the muscle cells, with subsequently impaired glucose phosphorylation and decreased insulin-stimulated glycogen synthesis [52,68,69] (Figure 17.1). Thus, lipids cause insulin resistance in humans via direct inhibition of glucose transport, but not via inhibition of the PDH complex [52,70,71]. Some studies [72,73], but not others [74], suggest that lipid-induced insulin resistance may be more pronounced in men than in women, which would support the known greater diabetes risk for men.

Increases in intramyocellular TAGs are an even better predictor of insulin resistance in muscle and liver than circulating plasma fatty acids [37]. Indeed, lipid-induced insulin resistance is reflected by impaired insulin signalling via reduced tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1) [52,75], IRS-1-dependent phosphatidylinositol 3-kinase (PI3K) activation, and serine phosphorylation of Akt [76]. This could result from accumulation of intramyocellular long-chain fatty acyl-CoA (LCFA-CoA), diacylglycerols (DAGs), or ceramides [77] (Figure 17.1). Studies on transgenic and knockout animal models provide compelling evidence that fatty acid elevation increases intramyocellular LCFA-CoA, CoA, and DAGs, but not ceramide content, along with stimulation of TAG synthesis by DAG *O*-acyltransferase-1 (DGAT-1) and of protein kinase C-θ (PKCθ), with subsequent serine phosphorylation of IRS-1 via the serine–threonine kinase cascade [78,79]. However, studies employing other animal models showed that the ceramide pathway could also be involved in lipid-induced insulin resistance [80–82]. Several studies in humans reported conflicting results, likely due to differences in the design, cohorts, and analytical methods [73,83,84]. A recent study shed more light on the time course of events of lipid-induced insulin resistance by performing serial biopsies in humans during lipid infusion and comparing the results obtained from biopsies from insulin-resistant individuals with obesity or type 2 diabetes [74]. Lipid infusion resulted in a transient increase in intramyocellular DAGs, followed by activation of PKCθ and increased phosphorylation of the serine^{1101} residues of IRS-1, with subsequent inhibition of insulin signalling and insulin-stimulated muscle glucose disposal (Figure 17.1). Similar increases in myocellular DAGs and PKCθ activation were found in individuals with type 2 diabetes and obesity without lipid infusion. DAG subspecies containing C_{18}-acyl residues correlated best with insulin resistance in all conditions of insulin resistance, whereas total ceramides and their subspecies were not affected either by lipid infusion or in people with the insulin resistance of obesity and type 2 diabetes [74].

In addition to lipids, dietary excess of protein has been related to insulin resistance [85] and circulating branched-chain amino acids predict type 2 diabetes [86]. By analogy with fatty acids, short-term elevation of plasma amino acids reduces insulin-stimulated glucose-6-phosphate and glycogen synthesis [85] by activating the mammalian target of the rapamycin (mTOR)/p70 S60 kinase pathway, with subsequent serine phosphorylation of IRS-1 [87,88]. This pathway would further favour ectopic lipid storage [89].

In conclusion, the lipid-induced insulin resistance or lipotoxicity hypothesis proposes that in the absence of a balance between fatty acid delivery and muscle TAG synthesis via DGAT-1 as well as oxidation in the mitochondria, lipotoxic species such as *sn*-1,2-DAGs will accumulate in the plasma membrane and activate PKCε/PKCθ in skeletal muscle [90]. This in turn will inhibit the insulin receptor kinase (IRK) activity (PKCε) and IRS-1–associated PI3K (PKCθ), leading to impaired insulin signalling and impaired insulin-stimulated glucose uptake. Any mechanism by which lipid delivery to the muscle is reduced, lipid oxidation is increased, and/or TAG synthesis is stimulated will likely reduce LCFA-CoA and plasma membrane *sn*-1,2-DAG concentrations and prevent lipid-induced muscle insulin resistance.

Consequently, decreases in muscle lipid oxidation could serve as another contributor to lipid accumulation in the skeletal muscle and thereby insulin resistance. Flux rates through muscle ATP synthase, reflecting basal mitochondrial phosphorylation, are ~40% lower in lean insulin-resistant first-degree relatives of individuals with type 2 diabetes than in insulin-sensitive but otherwise matched people [91]. During insulin stimulation, muscle ATP synthase flux doubled in insulin-sensitive humans, but was almost abolished in the offspring of people with type 2 diabetes [55]. Similarly, individuals with type 2 diabetes, but without obesity, featured ~25% lower mitochondrial phosphorylation rates in the basal (fasting) state [59,92] and no increase during insulin stimulation, even in the presence of increased availability of glucose as a substrate [59,92]. This may be due to reduced capacities of the electron-transport chain and/or the phosphorylation system [92] and/or reduced insulin-stimulated phosphate transport into the myocytes.

Ageing, an important risk factor of type 2 diabetes, associates with impaired biogenesis and accelerated apoptosis of mitochondria [93]. Non-obese older humans are not only frequently insulin resistant, but also feature higher intramyocellular TAG contents and ~30–40% lower rates of both muscle ATP synthase flux and tricarboxylic acid (TCA) cycle oxidation [94,95]. Hence age-associated reductions in mitochondrial function may predispose older people to ectopic lipid accumulation and muscle insulin resistance [94], possibly owing to damage by accumulating reactive oxygen species (ROS). In line with this contention, similar reductions were reported for neural mitochondrial activity in healthy older individuals [96]. The hypothesis of age-associated

ROS-induced reductions in mitochondrial function contributing to age-associated muscle insulin resistance was further supported by findings in transgenic mice with overexpression of human catalase targeted to the mitochondria (MCAT mice) [97]. These mice were protected from age-associated abnormalities in muscle mitochondrial function and DAG/PKCθ-induced muscle insulin resistance, along with reduced mitochondrial oxidative damage, preserved muscle ATP synthesis, and adenosine 5′-monophosphate-activated protein kinase (AMPK)-induced mitochondrial biogenesis [98, 99]. Moreover, measurements of basal and insulin-stimulated rates of muscle PDH (V_{PDH}) flux relative to citrate synthase flux (V_{CS}) employing [1-^{13}C] glucose incorporation into glutamate relative to alanine in muscle biopsies from healthy, lean, old, and young humans revealed a blunted rise of insulin-stimulated V_{PDH}/V_{CS} fluxes in the old people, along with 25% lower muscle glucose uptake and 70% higher accumulation of intramyocellular TAGs [100]. These findings indicate a marked inability of mitochondria to switch from lipid to glucose oxidation during insulin stimulation. Recent assessments of V_{PDH}/V_{CS} ratios in soleus or quadriceps muscles revealed that mitochondrial substrate preference, often referred to as *metabolic inflexibility*, is not essential for the pathogenesis of insulin resistance in humans [90]. Taken together, combined acquired and age-associated reductions in features of mitochondrial function may promote intramyocellular lipid accumulation and insulin resistance in type 2 diabetes.

In addition to ageing *per se*, other metabolic factors such as hyperglycaemia and dyslipidaemia may impair mitochondrial function and thereby contribute to muscle insulin resistance. In this context, insulin-resistant individuals with type 1 diabetes have lower insulin-stimulated ATP synthase flux, which negatively relates to glucometabolic regulation [56]. Short-term lipid infusion also leads to lower muscle ATP synthase flux, but only on the onset of insulin resistance in healthy humans [101]. The reduced rates of insulin-stimulated ATP synthase flux were associated with impaired insulin-stimulated increases in muscle glucose-6-phosphate concentrations due to lower insulin-stimulated glucose uptake [101, 102]. Lipid lowering via inhibition of lipoprotein lipase (LPL) by acipimox improves insulin resistance independently of changes in oxidative capacity in type 2 diabetes [103]. These findings suggest that glucose- and lipid-induced abnormalities in muscle mitochondrial function are not primary events in the development of insulin resistance in common type 2 diabetes.

A series of studies addressed the role of mitochondrial function independently of age and glycaemic levels [90, 104]. Young, lean, but severely insulin-resistant first-degree relatives of people with type 2 diabetes were identified with 30% lower basal rates of muscle ATP synthase and TCA cycle fluxes compared to age- and body mass–matched insulin-sensitive individuals [90]. This abnormality of mitochondrial oxidative phosphorylation was found in the presence of 38% lower mitochondrial density, indicating that the reduction in mitochondrial function may be attributed to lower muscle mitochondrial content [105]. In contrast to previous reports on skeletal muscle of people with type 2 diabetes [106, 107], this was not explained by reduced expression of the peroxisome proliferator-activated receptor (PPAR) γ-coactivator 1α (PGC1α) [105], a key regulator of mitochondrial biogenesis. Likewise, in another cohort of first-degree relatives of individuals with type 2 diabetes, the stimulatory effect of exercise training on insulin sensitivity and ATP synthesis did not depend on common single-nucleotide polymorphisms (SNPs) of PGC1α, but was modified by a G/G-SNP of the gene encoding NADH dehydrogenase (ubiquinone) 1β subcomplex (*NDUFB6*), a component of complex I of the mitochondrial respiratory chain [108]. The finding that the insulin resistance in relatives of individuals with type 2 diabetes is related to lower fasting and insulin-stimulated rates of muscle ATP synthesis in a similar fashion as in people with overt type 2 diabetes strongly underlines the role of inherited factors in the pathogenesis of insulin resistance and type 2 diabetes [59, 109]. Taken together, at least in this cohort of insulin-resistant first-degree relatives of individuals with type 2 diabetes, it is likely that a reduction in mitochondrial content, due to reduced mitochondrial biogenesis, is responsible for the reduced mitochondrial oxidative and phosphorylation activity and may be an acquired abnormality [110, 111]. Nevertheless, given the key role of mitochondrial activity in the regulation of fat metabolism in muscle cells [112–116], these data suggest that the reduced mitochondrial function may be an important predisposing factor that promotes plasma membrane *sn*-1,2-DAG accumulation in muscle cells and insulin resistance in muscle among people with insulin resistance whose parents have type 2 diabetes.

Insulin resistance in the liver

The liver plays a key role in the transition from the fasted to the fed state by its unique ability to switch rapidly from a glucose-producing organ to a glucose-storing organ. After ingestion of a mixed meal, the liver suppresses glucose production and takes up glucose for storage in the form of glycogen [117, 118]. In insulin-resistant individuals with type 2 diabetes, the excessive postprandial hyperglycaemia results from impaired suppression of glucose production along with ~45% lower hepatic glycogen accumulation than in healthy people [49]. This cannot be explained simply by the impaired prandial insulin secretion, but rather results from other mechanisms such as defective insulin-stimulated flux through glycogen synthase, because this abnormality persists during hyperinsulinaemic–hyperglycaemic clamps, which maximally favour glycogen synthesis [49]. Insulin-mediated hepatic glycogen synthesis correlates inversely with ectopic lipid content in the liver not only in people with type 2 diabetes but also in those without, in line with a close link between hepatic lipid content and hepatic insulin resistance [49, 95]. Hepatic lipid accumulation, previously termed steatosis, is another form of ectopic lipid accumulation and is now included in the definition of non-alcoholic fatty liver disease (NAFLD). Steatosis relates closely to whole-body insulin resistance and is present in obesity, the metabolic syndrome, and women with a history of gestational diabetes or with type 2 diabetes [119, 120]. Although it has been discussed that NAFLD develops in the setting of or secondary to prevailing insulin resistance [121, 122], increased lipid availability *per se* could also induce hepatic TAG storage and insulin resistance [38]. This hypothesis is supported by human studies where short-term lipid infusions caused hepatic insulin resistance, as reflected by impaired insulin-mediated suppression of glucose production [123]. Animal models indicate that lipid intermediates such as plasma membrane *sn*-1,2-DAGs also inhibit insulin signalling in the liver, similarly to the mechanism of lipid-induced insulin resistance in skeletal muscle [1, 78, 84] (Figure 17.2). One study in particular, inducing selective hepatic steatosis in rats by a

three-day high-fat diet, found that hepatic insulin resistance corresponds to impaired tyrosine phosphorylation of IRS-2 and increased activities of PKCε and c-Jun N-terminal kinase (JNK) 1, which act as serine/threonine kinases and can phosphorylate serine residues of IRS-2 [124]. One study of human liver biopsies detected increases in some PKC isoforms (ε, α, and ζ) in people with type 2 diabetes and obesity [125]. Another human liver biopsy studied found that stearoyl-CoA desaturase 1 (SCD1) activity and DAGs, but not ceramides, positively correlated with hepatic fat content [126]. Recent intraoperative liver biopsy studies provided evidence that increases in hepatic DAG content [127, 128] and PKCε activity [127] correlate negatively with hepatic insulin sensitivity in individuals with NAFLD and obesity, thereby underlining a critical role of the DAG/PKCε pathway also in hepatic insulin resistance in humans (Figure 17.2). More recently Petersen et al. demonstrated that PKCε-induced phosphorylation of the insulin receptor on threonine^{1160} (threonine^{1150} in mice) was necessary for lipid-induced hepatic insulin resistance [129], and using a cell fraction method Lyu et al. demonstrated that it was the plasma membrane–bound *sn*-1,2-diaglycerols that were responsible for the activation of PKCε and that PKCε is both necessary and sufficient for mediating lipid-induced hepatic insulin resistance [130]. This study also found that hepatic ceramide content did not consistently track with hepatic insulin resistance, suggesting that ceramides, like triglycerides, do not mediate hepatic insulin resistance.

Although NAFLD is most often associated with obesity, there are important exceptions where NAFLD and hepatic insulin resistance coexist in lean individuals [131, 132]. Healthy, young, lean Asian Indian men have a markedly greater risk of hepatic steatosis associated with hepatic insulin resistance than men of other ethnic groups [133]. Two polymorphisms (rs2854116 and rs2854117) in the apolipoprotein C3 (*ApoC3*) gene seem to predispose these individuals and lean men of Asian ethnic backgrounds to NAFLD and insulin resistance [134]. In these carriers of the APOC3 variant alleles (C-482T, T-455C, or both), higher fasting plasma apolipoprotein C3 and plasma TAG concentrations are 30% and 60% higher, respectively, than in wild-type homozygous humans. These findings can be explained in part by the inhibitory effect of apolipoprotein C3 on LPL activity, resulting in reduced plasma triglyceride clearance, leading to increases in post-prandial hypertriglyceridaemia and increased post-prandial chylomicron remnants. This mechanism was validated genetically in transgenic mice with hepatic overexpression of human *ApoC3*, which were more prone to develop hepatic steatosis than their wild-type littermate counterparts when fed a high-fat diet [135]. This *ApoC3* gene–environment interaction has only been observed in male individuals, likely reflecting a protective effect of oestradiol on inhibition of LPL activity [136]. Furthermore, this *ApoC3* gene–environment interaction is not observed in individuals with obesity, in whom this relatively subtle gene–environment effect to promote hepatic steatosis in lean individuals is masked by the dominant effect of obesity and insulin resistance to promote NAFLD [137].

A genome-wide association study identified a missense mutation I148M within patatin-like phospholipase domain containing 3 (PNPLA3/adiponutrin) that is more prevalent in Hispanic individuals and associates with NAFLD [138]. The rs738409 polymorphism of PNPLA3 also leads to impaired TAG hydrolysis [139]. Although the association between this polymorphism and hepatic steatosis has been reproduced in other populations, there is no association with insulin resistance, with the limitation of these studies that all the participants had obesity and were likely insulin resistant [140]. Individuals with the severe insulin-resistant diabetes endotype more likely carry the risk allele of this PNPLA3 polymorphism [141]. These individuals also feature markedly higher adipose tissue insulin resistance, suggesting a role of PNPLA3 for adipose tissue function [141]. Finally, alterations in other genes that regulate lipogenesis leading to lipodystrophy (e.g. *AGPAT2*, *PPARγ*) [142] or lipolysis (e.g. perilipin, *ATGL*, *CGI-58*) [143] may also lead to ectopic lipid deposition and insulin resistance. Hence there is growing evidence that gene–environment interactions can predispose even lean individuals to hepatic insulin resistance, NAFLD, and type 2 diabetes. There are a few exceptions in which ectopic lipid content dissociates from insulin resistance. A mutation in the *ABHD5* gene with consecutive deficiency in the protein comparative gene identification 58 (CGI-58) leads to Chanarin–Dorfman syndrome [94, 96, 97], which is characterized by excessive lipid deposition in the liver, muscle weakness, and central nervous symptoms in the absence of insulin resistance. In this condition, DAGs are restricted to storage in lipid droplets (and not the plasma membrane) and thereby cannot promote PKCε translocation to the plasma membrane, which is required for its binding to the insulin receptor and inhibition of IRK activity/insulin signalling in the liver.

Similar to skeletal muscle, people with type 2 diabetes but without obesity also show reductions in hepatocellular ATP concentrations as measured with non-invasive ^{31}P NMR methods [144] compared with age-matched and young people without diabetes [145]. Hepatocellular ATP and inorganic phosphate levels differently change in type 2 diabetes and type 1 diabetes over the initial five years after clinical diabetes onset [146]. Even with adjustments for liver fat content, hepatic ATP concentrations correlated closely with hepatic insulin sensitivity, but not with whole-body insulin sensitivity. People with type 2 diabetes but without obesity also had 40% lower flux rates through hepatic ATP synthase, which relate to both peripheral and hepatic insulin sensitivity but negatively with body fat content [147]. Nevertheless, other features of hepatic mitochondrial function are not uniformly impaired in insulin-resistant humans [148–150]. Using high-resolution respirometry to quantify directly mitochondrial respiration in liver biopsies, it was found that, despite similar mitochondrial contents, people with obesity with or without steatosis had 4.3–5.0-fold higher maximal respiration rates in isolated mitochondria than lean people, whereas people with non-alcoholic steatohepatitis (NASH) featured 30–40% lower maximal respiration associated with greater hepatic insulin resistance [151] (Figure 17.3). These individuals also had higher degrees of mitochondrial uncoupling and leaking activity, together with augmented hepatic oxidative stress paralleled by reduced antioxidant defence capacity and increased inflammatory response. These findings suggest an adaptation of the liver at early stages of obesity-related insulin resistance, which is subsequently lost during the progression of NAFLD and insulin resistance. In line with this hypothesis, insulin-resistant individuals with steatosis and obesity had a sixfold greater increase in hepatic ATP concentrations than in lean insulin-sensitive individuals after ingestion of a single mixed meal [152].

Taken together, these findings suggest that loss of adaptation of hepatic energy metabolism to increased lipid flux from large visceral adipose tissue depots and/or adaptation-related hepatic oxidative stress could cause hepatic lipid accumulation and subsequent hepatic insulin resistance in the context of type 2 diabetes.

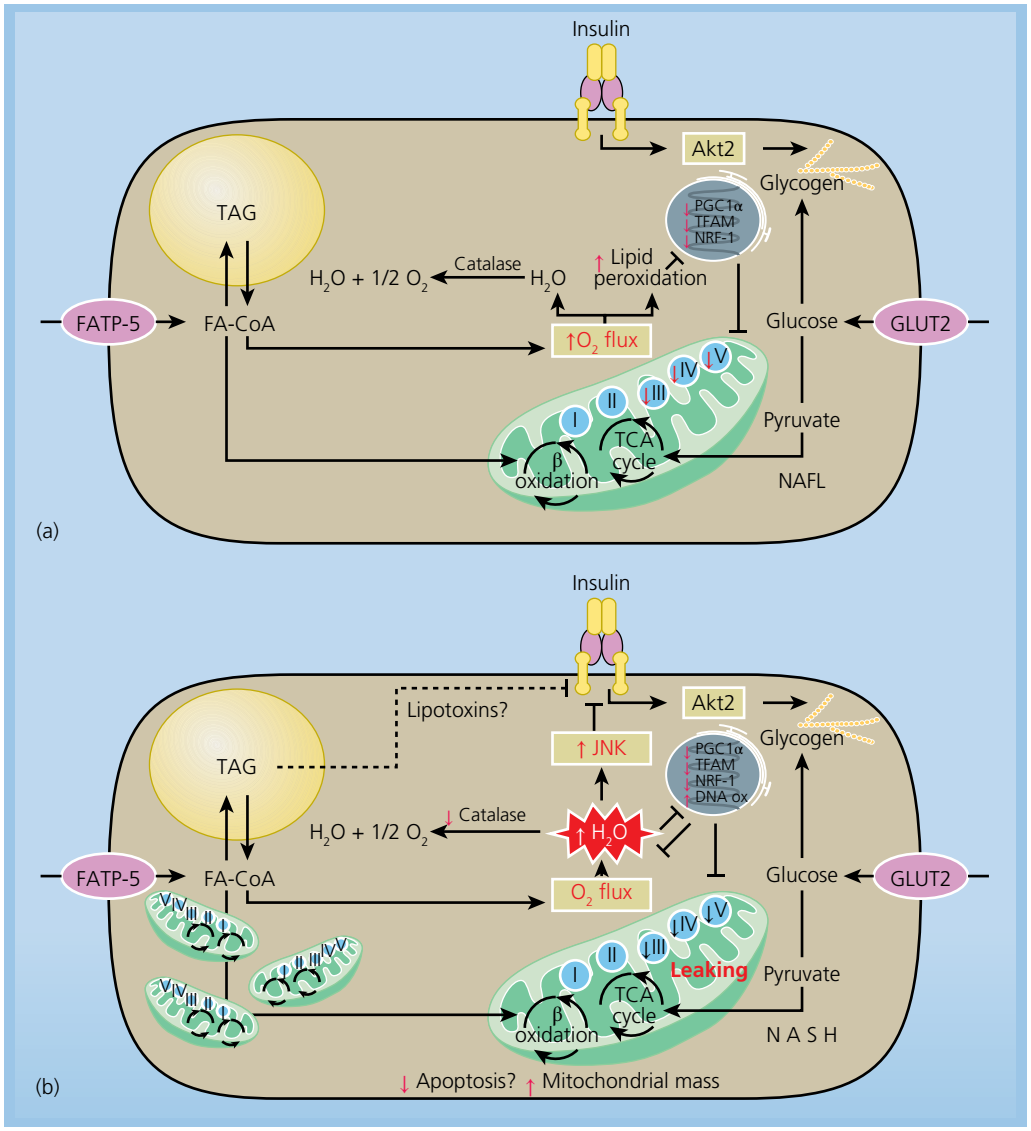

Figure 17.3 Hypothesis of adaptation of hepatic energy metabolism in the pathogenesis of non-alcoholic fatty liver disease and progression of hepatic insulin resistance. (a) In states of obesity, increased fatty acid delivery upregulates hepatic mitochondrial oxidative capacity, which prevents excessive storage of triacylglycerols (TAGs), but promotes the accumulation of reactive oxygen species and lipid peroxides, which are scavenged by hepatic catalase activity. (b) During the development of non-alcoholic fatty liver disease (NAFLD), the efficiency of mitochondrial coupling fails, which accelerates the generation of hydrogen peroxide (H_2O_2) in the face of decreasing catalase activity. Finally, oxidative stress decreases mitochondrial biogenesis, but increases leakage of mitochondria and activates c-Jun N-terminal kinase (JNK), which drives cellular inflammation and progression to steatohepatitis (NASH). Source: Koliaki et al. 2015 [143]. Copyright 2015 Elsevier.

Insulin resistance in adipose tissue

Adipose tissue is highly sensitive to the action of insulin on lipolysis in healthy humans, but not in states of insulin resistance and type 2 diabetes [153–155], which are also characterized by elevations in plasma concentrations of TAGs and fatty acids. These alterations will contribute to lipid-mediated effects on insulin sensitivity in other organs such as liver and skeletal muscle. By contrast, obesity and the metabolic syndrome have been linked to a state of so-called *subclinical inflammation*, arising from adipose tissue and leading to an imbalance of the secretion of adipocytokines with anti-inflammatory and insulin-sensitizing properties such as adiponectin and proinflammatory cytokines such as leptin, tumour necrosis factor-α, and interleukin-6 (IL-6), and many others [156] (Figure 17.4). The latter adipocytokines may cause insulin resistance in liver and muscle by stimulating increased serine phosphorylation of IRS1 by activation of JNK1 and activation of Iκ kinase β (IKKβ)–nuclear factor-κB (NF-κB) kinase β, both of which are involved in chronic insulin resistance. Anti-inflammatory treatment, either acutely with acetyl salicylate or chronically with salsalate, promotes a modest improvement in glycaemic levels and insulin resistance in people with type 2 diabetes and obesity [157, 158], indicating that activation of inflammatory pathways can contribute to obesity-associated insulin resistance and hyperglycaemia in type 2 diabetes. Endoplasmic reticulum stress may serve as another cause of cellular inflammation and insulin resistance via JNK activation [159, 160]. In humans, weight loss following bariatric surgery

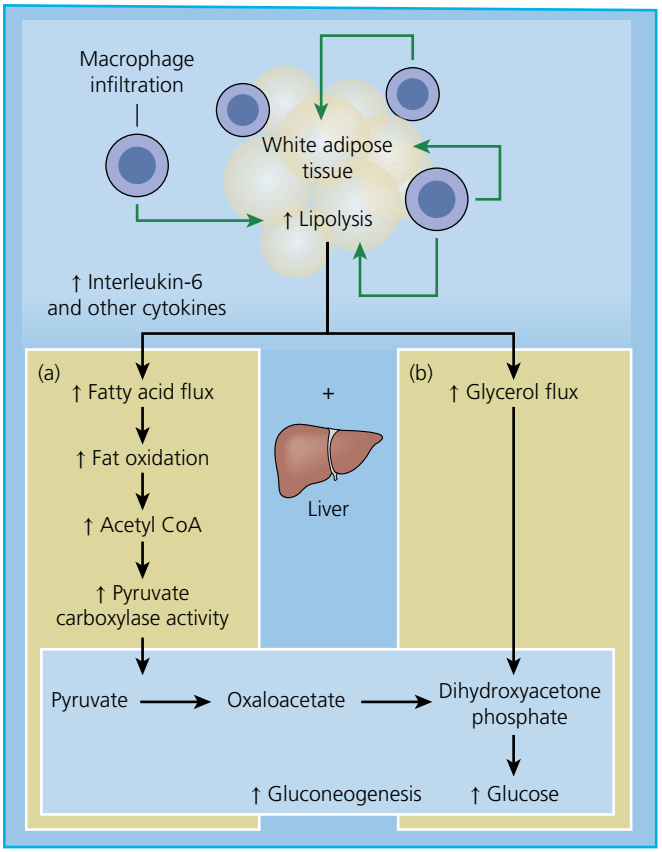

Figure 17.4 Hypothesis of macrophage-induced lipolysis in the pathogenesis of fasting hyperglycaemia and insulin resistance. During the development of obesity, macrophage infiltration of white adipose tissue results in increased lipolysis by release of macrophage-derived cytokines such as interleukin-6. Increased rates of lipolysis lead to accelerated rates of hepatic gluconeogenesis by two mechanisms. (a) First, increased fatty acid delivery to the liver leads to higher hepatic acetyl-coenzyme A (CoA) levels when its production through fat oxidation exceeds its rates of oxidation in the tricarboxylic acid cycle. This leads to increased pyruvate carboxylase activity. (b) Second, increased delivery of glycerol promotes its conversion to dihydroxyacetone (glyceraldehyde) 3-phosphate, which serves as a precursor of glucose. Source: Shulman 2014 [1]. Copyright © 2014 Massachusetts Medical Society. Reprinted with permission.

improves insulin sensitivity [153, 157], which has been further associated with altered gut microbiota or hormone secretion [161] and also with reductions in endoplasmic reticulum stress. These hypotheses are currently under further investigation. Finally, chronically increased lipid availability may also cause mitochondrial and endoplasmic reticulum stress with release of ROS, which in turn activate proinflammatory NF-κB [26]. Under these conditions, intracellular lipid metabolites (DAGs, ceramides, acyl-CoA) may also contribute to the resulting insulin resistance [71, 162, 163]. In support of the latter possibility, Lyu et al. recently demonstrated that increases in plasma membrane *sn*-1,2-DAGs and activation of PKCε leading to insulin receptor threonine^{1150} phosphorylation were responsible for lipid-induced white adipose tissue insulin resistance following short-term high-fat feeding in rodent [130]. These findings underline the relevance of the plasma membrane *sn*-1,2-DAG/PKCε/IRK^{T1160} pathway in mediating lipid-induced insulin resistance in multiple insulin-responsive tissues (liver, skeletal muscle, white adipose tissue).

Syndromes of lipodystrophy or lipoatrophy made it possible to study the roles of peripheral or visceral adipose tissues for insulin resistance and ectopic lipid deposition [131, 164–166]. Both inherited and acquired forms of generalized lipodystrophy are devoid of relevant amounts of adipose tissue and develop excessive hypertriglyceridaemia and ectopic fat deposition owing to fat overflow from the negligible triglyceride storage in adipocytes. Furthermore, these individuals have lower levels of inflammatory cytokines and leptin, resulting in hyperphagia [132]. Individuals with severe, generalized lipodystrophy have severe steatosis along with hepatic and muscle insulin resistance or even overt type 2 diabetes, which completely resolves after 3–8 months of leptin replacement therapy, as demonstrated previously in rodent models of lipodystrophy [78, 84]. Thus, visceral lipid content is likely more of a marker of hepatic steatosis rather than a causal player in the development of insulin resistance [132].

Although these findings also demonstrate that the important role of lipid-induced alterations at the onset of insulin resistance can be dissociated from inflammation, they do not exclude the operation of other mechanisms promoting the progression to impaired glucose tolerance and fasting hyperglycaemia. According to the canonical view, impaired pancreatic β- and α-cell function first leads to reduced hepatic activation of Akt and exclusion of forkhead box (FOXO1) from the nucleus of the hepatocyte, with consequent transcription-mediated hepatic gluconeogenesis [167]. Second, subclinical inflammation would diminish insulin action through secreted (adipo)cytokines, which subsequently interfere with insulin signalling and increase hepatic gluconeogenic protein transcription by activating the NF-κB/JNK/ceramide pathways. Recently, an alternative mechanism has been proposed, by which macrophage-induced lipolysis may regulate hepatic gluconeogenesis independently of canonical insulin receptor signalling and thereby link subclinical inflammation to the onset of fasting hyperglycaemia [1, 168] (Figure 17.4). Using a novel *in vivo* metabolomics approach in rodent models, it was demonstrated that IL-6 and TNF-α, released from macrophages within adipose tissue, inhibit insulin-mediated lipolysis in white adipose tissue with augmented delivery of fatty acids and glycerol to the liver [169]. This resulted in increased hepatic acetyl-CoA concentrations, due to increased fatty acid β-oxidation, which stimulated hepatic gluconeogenesis through allosteric activation of pyruvate carboxylase as well as increased glycerol conversion to glucose in the liver by a substrate push mechanism. In line with these studies in rodents, insulin-resistant adolescents with obesity displayed increased circulating IL-6 concentrations and a more marked, 50% rise in IL-6 concentration in white adipose tissue, along with impaired insulin-mediated suppression of white adipose tissue lipolysis and endogenous glucose production compared with age- and body mass–matched insulin-sensitive humans. These studies collectively support the concept of an indirect action of insulin on hepatic glucose production via adipocytes [170, 171]. Some further observations underline that transcriptional control of hepatic gluconeogenesis cannot be due simply to direct insulin action on the liver to suppress glucose release. Insulin-mediated reduction in endogenous glucose production occurs rapidly, within minutes, even in individuals with type 2 diabetes [37], and there is a lack of any relationship between hepatic expression of gluconeogenic protein and fasting hyperglycaemia in humans with obesity, with and without type 2 diabetes [127].

Stepwise development of tissue-specific insulin resistance

The close association between obesity, ectopic fat accumulation, and insulin resistance makes it difficult to identify skeletal muscle, liver, or adipose tissue as the primary cause of insulin resistance. Indeed, ingestion of one energy-dense high-fat meal can cause simultaneous insulin resistance in these tissues both in humans and in mice [172]. Nevertheless, in humans the earliest development of insulin resistance most likely occurs in the adipose tissue [91,173] (Figure 17.4). The observation of rapid reversibility of hepatic but not muscle insulin resistance with moderate weight loss in individuals with NAFLD, and leptin replacement in generalized lipodystrophy [132] and type 2 diabetes [131], is in agreement with this contention. As detailed earlier, the principal mechanism involves tissue-specific accumulation of plasma membrane *sn*-1,2-DAGs, which occurs owing to an imbalance between substrate influx and oxidation (mitochondrial activity) and/or synthesis of TAGs in insulin-responsive tissues. Accordingly, any situation that will disrupt the balance between delivery and removal of plasma membrane *sn*-1,2-DAGs to the muscle, liver, and white adipose tissue will lead to the accumulation of these lipid species, resulting in activation of PKCε (as well as PKCθ in skeletal muscle) and insulin resistance. This likely explains the high prevalence of obesity-associated insulin resistance, where lipid delivery exceeds storage and oxidation, the impaired adipocyte storage capacity in lipodystrophy, and the decreased substrate oxidation in certain forms of inherited insulin resistance such as lean, insulin-resistant relatives of individuals with type 2 diabetes or in acquired insulin resistance occurring during ageing [140].

Evidence for the specific role of inefficient substrate oxidation during the onset of insulin resistance comes from the human model of lean, young, severely insulin-resistant relatives of people with type 2 diabetes, who are devoid of any other confounding factors such as obesity, hyperglycaemia, or subclinical inflammation. In these individuals, inherited abnormalities in muscle mitochondrial biogenesis and/or function can cause or at least contribute to muscle insulin resistance due to decreased mitochondrial fatty acid oxidation and subsequent accumulation of intracellular lipid metabolites (plasma membrane *sn*-1,2-DAGs) with diminished insulin signalling [105,174]. The impaired adaptation of insulin sensitivity to exercise training in carriers of the rs540467 polymorphism of the *NDUFB6* gene in such relatives of people with type 2 diabetes is in line with this hypothesis [108]. Likewise, the rs2267668 A/G SNP in the *PPARD* gene and the Gly482Ser SNP in the *PGC1A* gene also have independent and additive effects on the effectiveness of aerobic exercise training to increase physical fitness and insulin sensitivity in humans at risk for type 2 diabetes [175]. Impaired mitochondrial function as assessed from ATP synthesis was also found in other non-obese groups at increased risk for type 2 diabetes, such as individuals with previous acromegaly [176] or gestational diabetes [120]. All these alterations in skeletal muscle metabolism would lead to lower rates of insulin-stimulated glucose disposal and accelerated rates of anaerobic glycolysis with release of lactate and alanine as substrates of hepatic gluconeogenesis.

Chronic overnutrition will increase the size of white adipose tissue and recruit macrophages to adipose tissue. Local inflammation of adipose tissue leads to macrophage-induced lipolysis with release of TAGs and fatty acids, which in turn elevate the white adipose tissue–derived hepatic acetyl-CoA pool and drive hepatic gluconeogenesis. This mechanism could potentiate the transition from whole-body insulin resistance to impaired glucose tolerance and type 2 diabetes. Chronic increases in hepatic gluconeogenesis would then impair insulin secretion by the pancreatic β cells and inappropriate glucagon secretion by the α cells due to glucose toxicity, and ultimately exacerbate both fasting and post-prandial hyperglycaemia in the context of overt type 2 diabetes.

Finally, excessive flux of fatty acids to the liver will promote NAFLD through increased hepatic esterification, which occurs in a mostly insulin-independent manner and therefore is not dependent on postulating *selective hepatic insulin resistance* [177]. Hepatic mitochondria may transiently adapt to the increased substrate availability by upregulating their oxidative capacity at the expense of decreased coupling efficiency until NAFLD develops [150]. Ongoing substrate overloading will blunt the liver's antioxidant capacity and increase hepatic oxidative stress, with subsequent leakage of mitochondria and decreased mitochondrial biogenesis, resulting in NASH and aggravated insulin resistance.

Several studies provided experimental support for the concept of the stepwise development of insulin resistance in humans (Figure 17.5). Monitoring energy distribution employing $^{13}C/^{1}H$ NMR spectroscopy and hepatic *de novo* lipogenesis after ingestion of

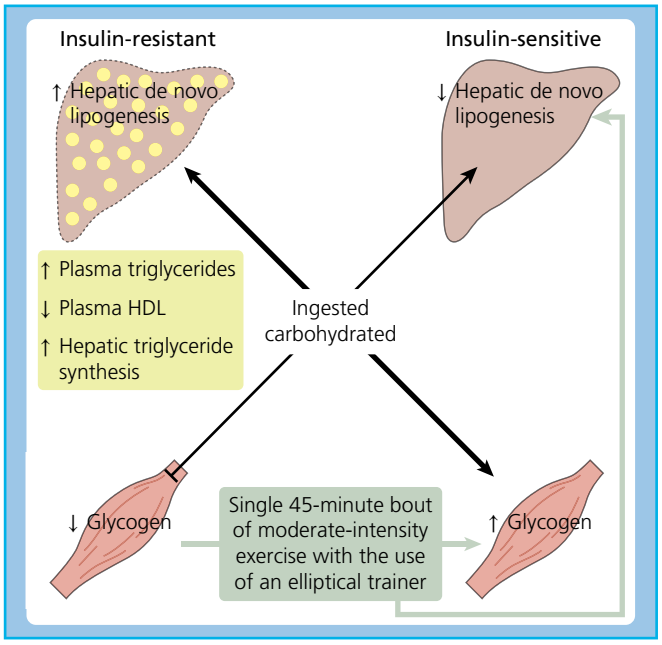

Figure 17.5 Concept of the stepwise development of insulin resistance from skeletal muscle to atherogenic dyslipidaemia and non-alcoholic fatty liver disease. In healthy, young, lean people, selective insulin resistance in skeletal muscle results in the diversion of ingested carbohydrates from muscle glycogen synthesis to the liver. Combined with compensatory hyperinsulinaemia, this stimulates hepatic *de novo* lipogenesis, synthesis of triglycerides, and secretion of very low-density lipoproteins (VLDL), resulting in hypertriglyceridaemia and reduced plasma high-density lipoprotein (HDL) levels. It is of note that even one bout of exercising is able to restore the abnormal pattern of energy storage after carbohydrate ingestion by stimulating glucose uptake and glycogen synthesis in muscle through insulin-independent adenosine 5′-monophosphate-activated protein kinase (AMPK) activation of glucose transporter 5 (GLUT4) recruitment, and further improves hepatic carbohydrate and lipid metabolism. Source: Shulman 2014 [1]. Copyright © 2014 Massachusetts Medical Society. Reprinted with permission.

a high-carbohydrate meal revealed that post-prandial muscle glycogen synthesis was reduced by ~60% in insulin-resistant compared with insulin-sensitive young, lean individuals [177]. On the other hand, liver TAG content and hepatic *de novo* lipogenesis were doubled in the insulin-resistant group. This was accompanied by 60% higher plasma TAG and uric acid contents and 20% lower fasting HDL-C, but with no changes in circulating adipocytokines. These data confirmed that muscle insulin resistance *per se* shifts the distribution of post-prandial energy storage away from muscle glycogen and leads to upregulation of hepatic lipid synthesis and hepatic lipid storage and export of VLDL, thereby contributing to the development of atherogenic dyslipidaemia; these are features of the metabolic syndrome independently of visceral obesity or subclinical inflammation. Meal-dependent increases in liver glycogen synthesis were comparable in insulin-resistant and insulin-sensitive individuals, which is in accordance with the low amount of liver lipids and normal hepatic insulin sensitivity in these individuals with muscle insulin resistance [92, 178]. It is noteworthy that a single bout of moderate-intensity exercise abrogated the abnormal pattern of energy storage, which promoted muscle glycogen synthesis after carbohydrate ingestion through increased glucose transport activity [172, 179] (Figure 17.5). Moreover, non-obese insulin-resistant women with a history of gestational diabetes also feature doubled fasting liver TAGs without NAFLD, which correlates with insulin resistance and fat mass [120]. Hepatic, but not visceral, fat mass relates to hepatic insulin resistance and increased TAG release [180]. Finally, loss of adaptation of hepatic mitochondria to excessive substrate delivery may accelerate steatosis and promote the progression of NAFLD, which is a major and independent predictor of cardiovascular morbidity and mortality in the context of type 2 diabetes [181].

Conclusion

Insulin resistance is the initial event preceding type 2 diabetes by decades before the onset of any relevant insulinopaenia, which is required for the transition from normoglycaemia to fasting and post-prandial hyperglycaemia. Insulin resistance in insulin liver, muscle, and white adipose tissue can be attributed to increases in plasma membrane–bound *sn*-1,2-DAG, which accumulates in these tissues as ectopic lipid due to an imbalance between fatty acid delivery or synthesis versus intracellular metabolism by oxidation and/or storage as neutral lipid (triglyceride). Increases in plasma membrane–bound *sn*-1,2-DAG in turn lead to activation or translocation of PKCε in these tissues, which results in phosphorylation of the insulin receptor on threonine^{1160} and inhibition of IRK activity. Activated PKCε also phosphorylates many additional proteins, including p70S6K, which in turn will also contribute to insulin resistance downstream of the insulin receptor. In skeletal muscle, increases in plasma membrane–bound *sn*-1,2-DAG also result in activation/translocation of PKCθ, which phosphorylates IRS-1 and inhibits insulin signalling at the level of IRS-associated PI3K. Excess delivery of substrates (fatty acids) to muscle, which exceed rates of mitochondrial fatty acid oxidization and/or storage as triglycerides in the lipid droplet, is currently the most common reason for obesity and lipodystrophy-associated muscle insulin resistance. Under conditions of a positive energy balance, impaired muscle insulin action, due to this plasma membrane–bound *sn*-1,2-DAG/nPKC mechanism, distributes ingested carbohydrate away from muscle glycogen storage towards hepatic *de novo* lipogenesis, resulting in NAFLD, the metabolic syndrome, and type 2 diabetes. During the later stages of obesity, macrophage infiltration of the white adipose tissue causes local increases in cytokines (e.g. TNF-α, IL-6), which favour lipolysis, leading to increased flux of fatty acids and glycerol to the liver [173]. Greater fatty acid availability raises hepatic acetyl-CoA and the activity of pyruvate carboxylase, resulting in increased hepatic gluconeogenesis. Greater glycerol availability – via substrate push – stimulates glycerol conversion to glucose, thereby further increasing hepatic gluconeogenesis [173]. Increases in hepatic gluconeogenesis, on top of peripheral insulin resistance, lead to β-cell exhaustion, likely due to glucose toxicity and possibly other factors, which results in the transition from whole-body insulin resistance to impaired glucose tolerance and type 2 diabetes.

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18 Obesity and Diabetes

Nick Finer
National Centre for Cardiovascular Prevention and Outcomes, UCL Institute of Cardiovascular Science, London, UK

Key points

- Obesity is a chronic disease characterized by an abnormal or excessive accumulation of adipose tissue and biomechanical and metabolic complications.
- The huge rise in the prevalence of obesity over the past 50 years has driven the commensurate increase seen in type 2 diabetes.
- It is estimated that 89% of individuals with type 2 diabetes have obesity or overweight.
- The triad of obesity, type 2 diabetes, and non-alcoholic fatty liver disease (NAFLD) is well recognized.
- Body mass index (BMI), defined as weight in kg/(height in m)^2, is the most convenient population-level measure of overweight and obesity, but this has limitations when defining the clinical severity of excess weight.
- Waist circumference is commonly used as a surrogate of visceral fat accumulation, but imaging techniques with computer-assisted tomography or magnetic resonance imaging are the gold standard.
- The overlapping *epidemics* of obesity and type 2 diabetes have been considered as *syndemic*.
- Heritability for both obesity and type 2 diabetes is estimated to be moderate to high at between 30% and 70%.
- Insulin resistance correlates with visceral fat mass, total fat mass, BMI, and waist circumference, but to a much lesser extent with subcutaneous fat, emphasizing the importance of adipose distribution.
- The twin cycle model links obesity to the development of type 2 diabetes and explains how weight loss can reverse the process; positive energy balance promotes liver fat deposition. The process is promoted by insulin and results in decreased hepatic insulin sensitivity and increased hepatic glucose output, forming the first vicious cycle. The second vicious cycle results from a spillover of liver-derived triglyceride-rich, very low-density lipoprotein, which drives ectopic fat deposition in other tissues, including the pancreatic β cells. This impairs β-cell function and contributes to chronic hyperglycaemia.
- Therapeutic weight loss is a powerful intervention that can ameliorate or reverse many of the metabolic abnormalities present in people with diabetes.
- Very low-energy diets can lead to diabetes remission and are associated with improvements in blood pressure, lipid abnormalities, carbohydrate metabolism, and cardiorespiratory function.
- The development of glucagon-like peptide (GLP-1) receptor agonists, already well established as treatments for type 2 diabetes, as well as dual agonists that combine GLP-1 and glucose-dependent insulinotropic peptide (GIP) agonism, has transformed, and is transforming, the potential for anti-obesity medications. They lead to ≥10% weight loss and prevent and reverse type 2 diabetes.
- Bariatric surgery with gastric bypass or sleeve gastrectomy improves glycaemia through a variety of mechanisms other than weight loss alone.

Obesity is now considered a chronic disease characterized by biomechanical and metabolic complications. While the link between obesity and ill health was first recognized 400 years BCE by Hippocrates and Hindu physicians [1], the specific link with diabetes is more recent [2], culminating in the now widely coined term *diabesity* that describes the association [3,4]. The huge rise in obesity prevalence in the past 50 years is now recognized to have driven the commensurate increase seen in type 2 diabetes incidence and prevalence. Obesity, a disease in its own right [5–7], was estimated by the World Health Organization (WHO) in 2016 to affect 650 million adults over the age of 18 years; 1.9 billion had overweight [8]. This represents 13% of all adults. Obesity in children and adolescents has increased even faster, such that 124 million children and adolescents (6% of all girls and 8% of all boys) are classified as having obesity. Compared to 1975, there has been a threefold increase in prevalence in adults and a six- to eightfold increase in children, but this masks large regional variations. The highest prevalence rates are in the USA (37% of all adults), Middle East (up to 35%), and Pacific islands (over 50%) [8]. It is estimated that 89% of individuals with type 2 diabetes have obesity or overweight [9]. The global prevalence of diabetes is estimated to reach 8.0% (454 million) by 2030, with type 2 diabetes accounting for ~90% of the total [10] driven by obesity [11] and an ageing population [10]. This chapter explores the pathophysiology of the disease of obesity, its links to diabetes, and its clinical management.

Obesity: definitions and phenotypes

Obesity is defined as an abnormal or excessive accumulation of adipose tissue that may impair health [5]. Adipose tissue is present throughout the body. As weight is gained, fats (lipids) are stored:

- In different adipose depots – subcutaneous, visceral, or intra-abdominal (e.g. omental and peri-renal).
- Ectopically – in tissues such as liver, muscle, heart, and pancreas and even in the vasculature and bone marrow.

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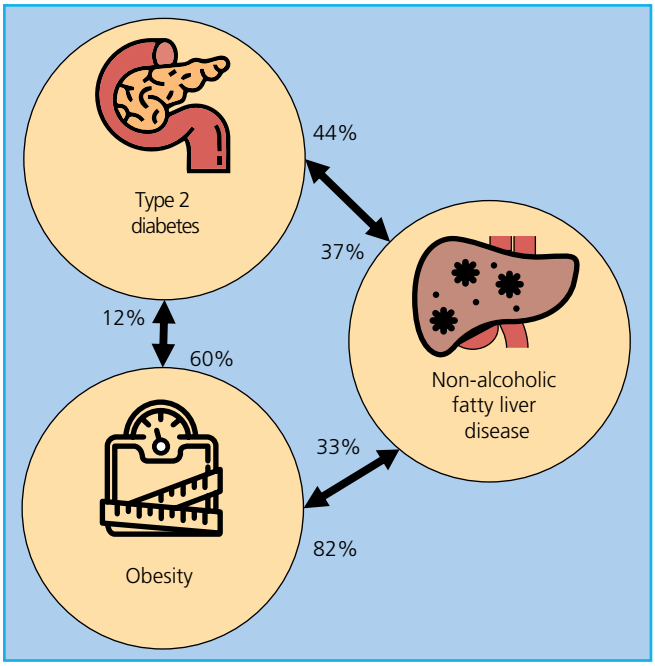

Figure 18.1 The prevalences of type 2 diabetes, obesity, and non-alcoholic fatty liver disease. Generally accepted epidemiological evidence suggests that, among people with non-alcoholic fatty liver disease (global prevalence: 5%–6%), 82% live with obesity, and 44% with type 2 diabetes; among those with type 2 diabetes (global prevalence in 2019: 9%, 463 million), 37% are estimated to have non-alcoholic fatty liver disease, and approximately 60% have obesity; for obesity (global prevalence: 35%, 650 million), 33% may have non-alcoholic fatty liver disease and 12% diabetes.

The triad of obesity, type 2 diabetes, and non-alcoholic fatty liver disease (NAFLD) is well recognized (Figure 18.1) [12]. NAFLD, defined by the presence of steatosis in ≥5% of hepatocytes after excluding other causes of fatty liver, includes a spectrum of conditions, ranging from hepatic steatosis to non-alcoholic steatohepatitis and liver fibrosis, which may progress to cirrhosis and hepatocellular carcinoma. The term metabolic (dysfunction)-associated fatty liver disease (MAFLD) is increasingly used, as it emphasizes the role of the metabolic dysfunction common (but not necessarily due) to obesity and diabetes [13].

Adipose tissue is not just an energy storage organ, but an active endocrine tissue secreting hormones such as leptin and adiponectin, as well as many adipocytokines that increase systemic and paracrine inflammation [14]. Operationally, body mass index (BMI), defined as weight in kg/(height in m)^2, is the most convenient population-level measure that estimates overweight and obesity. A BMI ≥30 kg/m^2 is considered to define obesity in people of white North European ancestry, while a BMI ≥25 kg/m^2 defines overweight (now termed pre-obesity). Different thresholds have been proposed for Asian (≥23 kg/m^2 pre-obesity, ≥25 kg/m^2 obesity) [15] and Japanese populations (≥25 kg/m^2) [16]. BMI has limitations when defining the clinical severity of excess weight, since at any given BMI there may be a threefold variation in % body fat [17]. Additionally, many factors, such as age, sex, ethnicity, muscle mass, illness, and weight loss, can alter the relationship between BMI and body fat. BMI does not give information about fat distribution [18]. Adipose tissue physiology differs considerably depending on its location, with visceral (intra-abdominal, peri-renal, and ectopic fat) most closely related to obesity complications. Epidemiologically many obesity complications, especially cardiometabolic and diabetes, correlate better with visceral fat accumulation than BMI [19–21]. While waist circumference or other anthropometric ratios (waist-to-hip and waist-to-height) [22,23] are commonly used as surrogates of visceral fat accumulation, imaging techniques with computer-assisted tomography or magnetic resonance imaging (MRI) are the gold standard [24].

Severity of obesity has been, rather arbitrarily, classified into BMI bands (Table 18.1). The recognition that fat distribution is of fundamental importance in determining the pathogenicity of obesity has led to the inclusion of waist circumference to improve the definition of risk within each BMI band (Table 18.1). More recent classifications (both of which include the presence of type 2 diabetes) are clinically rather than anthropometrically based. The Edmonton Obesity Staging System [27] is based on the presence of obesity-related risk factors or complications (Table 18.2) that correlate better than BMI with mortality [28,29], while the King's Obesity Staging Criteria (Table 18.3), albeit based on arbitrary criteria, can guide clinical management and assess responses to treatment [30].

Table 18.1 Classification of obesity and risk based on anthropometric measures.

	International classification [25]			Asian population[a] [15]	Japanese guidelines[a] [16]
Classification	**BMI kg/m^2**	**Waist circumference Men ≤102 cm Women ≤88 cm**	**Waist circumference Men >102 cm Women >88 cm**	**BMI kg/m^2**	**BMI kg/m^2**
Underweight	<18.5				<18.5
Normal range	≥18.5 to <25			≥18 to <23	≥18.5 to <25
Pre-obesity[a]	≥25 to <30	Increased	High	≥23 to <25	
Obesity	≥30			>25	
Obesity class I	≥30 to <35	High	Very high		≥25 to <30
Obesity class II	≥35 to <40	Very high	Very high		≥30 to <35
Obesity class III	≥40	Extremely high	Extremely high		≥35 to <40
Obesity class IV					≥40

[a] Waist circumference for different populations: Asian: men ≤102 cm, women ≤88 cm; Japanese: men >90 cm, women >80 cm [26].

Table 18.2 Edmonton staging system for obesity.

Stage	Definition
0	No apparent obesity-related risk factors, physical symptoms, psychopathology, functional limitations, and/or impairment of well-being
1	Obesity-related subclinical risk factor(s), e.g. borderline hypertension, impaired fasting glucose, elevated liver enzymes, etc., mild physical symptoms (e.g. dyspnoea on moderate exertion, psychopathology, functional limitations, and/or impairment of well-being)
2	Established obesity-related chronic disease(s), e.g. hypertension, type 2 diabetes, sleep apnoea, osteoarthritis, reflux disease, polycystic ovary syndrome, anxiety disorder, moderate limitations in activities of daily living and/or well-being
3	Established end-organ damage, e.g. myocardial infarction, heart failure, diabetes complications, incapacitating osteoarthritis, significant psychopathology, functional limitation(s), and/or impairment of well-being
4	Severe (potentially end-stage) disability/ies from obesity-related chronic disease disabling psychopathology, functional limitation(s), and/or impairment of well-being

The obesity and diabetes syndemic

The overlapping epidemics of obesity and type 2 diabetes have been considered as syndemic. As originally conceived, the term syndemic was introduced to bring 'new perspectives on the interaction between co-existing disorders in specific communities and with biological, behavioural and social factors that influence the occurrence and consequences of the diseases' [31]. Obesity and type 2 diabetes represent two types of adverse interaction clustering: a biological–biological interface and a biological–social interface (Figure 18.2) [32,33]. The former relates to common genetic and physiological factors that underlie both obesity and type 2 diabetes, while shared environmental factors include changes in nutrition, physical activity, and psychological health [34].

Heritability for both obesity and type 2 diabetes is estimated to be moderate to high at between 30% and 70% (Chapters 12 and 13) [35]. Genome-wide association studies have identified ~700 variants for obesity [36] and >400 for type 2 diabetes [37]. There is little shared genetic aetiology, which only accounts for ~15–20% of known heritability [38]. A report in 2015 listed 49 loci (33 new) associated with waist-to-hip ratio adjusted for BMI, and an additional 19 loci newly associated with related waist and hip circumference measures [39]. Many observational studies have shown correlations of obesity (and fat distribution) with type 2 diabetes [40,41], but do not in themselves allow inferences. The causal relationship between obesity and type 2 diabetes has been investigated, and established, using Mendelian randomization techniques. A polygenic risk score, based on 93 single-nucleotide polymorphisms (SNP) related to obesity in 119 859 individuals in the UK Biobank, found a near twofold increased risk for type 2 diabetes for each increase in BMI of 4.83 kg/m^2, findings replicated in a study of up to 213 556 individuals from 14 prospective studies and randomized trials and 4 consortia [42]. Genetic susceptibility to type 2 diabetes is mediated both through effects on insulin-release and insulin sensitivity [43]. Epigenetic effects, impairing β-cell function, are also well described and can be acquired *in utero*, or by exposure to lifestyle factors including inactivity and obesity [44].

Syndromic obesities are increasingly recognized and for many the genetic basis has been identified. Many of the 79 identified syndromes in which obesity is a feature (e.g. Prader-Willi, Bardet-Biedl, Alström syndromes) also include a high prevalence of type 2 diabetes [45]. Monogenic obesities are increasingly recognized, especially in children presenting with severe early-onset obesity, often with other features such as learning disability (Table 18.4) [46]. The development of specific treatments for a small minority of such obesities, some of which may progress to adulthood undiagnosed, emphasizes the increasing need for genetic diagnosis.

Pathophysiology of obesity and diabetes

The pathophysiology of type 2 diabetes is complex [47] and characterized by insulin resistance [48] and pancreatic insulin hypersecretion to overcome the insulin resistance early in the evolution of the disease. Both β-cell dysfunction and decreased insulin sensitivity are pivotal in the pathogenesis and progression of type 2 diabetes [49]. Insulin resistance drives accumulation of free fatty acids in target

Table 18.3 King's obesity staging criteria.

	Stage 0 Normal health	Stage 1 At disease risk	Stage 2 Established disease	Stage 3 Advanced disease
Airways	Normal	Snoring	Requires CPAP	Cor pulmonale
Body mass index (BMI) (kg/m^2)	<35	35–40	40–60	>60
Cardiovascular	<10% risk	10–20% risk	Heart disease	Heart failure
Diabetes	Normal	Impaired fasting glucose	Type 2 diabetes	Uncontrolled diabetes
Economic	Normal	Increased expenses	Workplace discrimination	Unemployed due to obesity
Functional	Can manage 3 flights of stairs	Can manage 1–2 flights of stairs	Requires walking aids or wheelchair	Housebound
Gonadal	Normal	Polycystic ovary syndrome	Infertility	Sexual dysfunction
Health – perceived	Normal	Low mood or quality of life	Depression	Severe depression
Image	Normal	Dislikes body	Body image dysphoria	Eating disorder with purging

CPAP, continuous positive airway pressure.

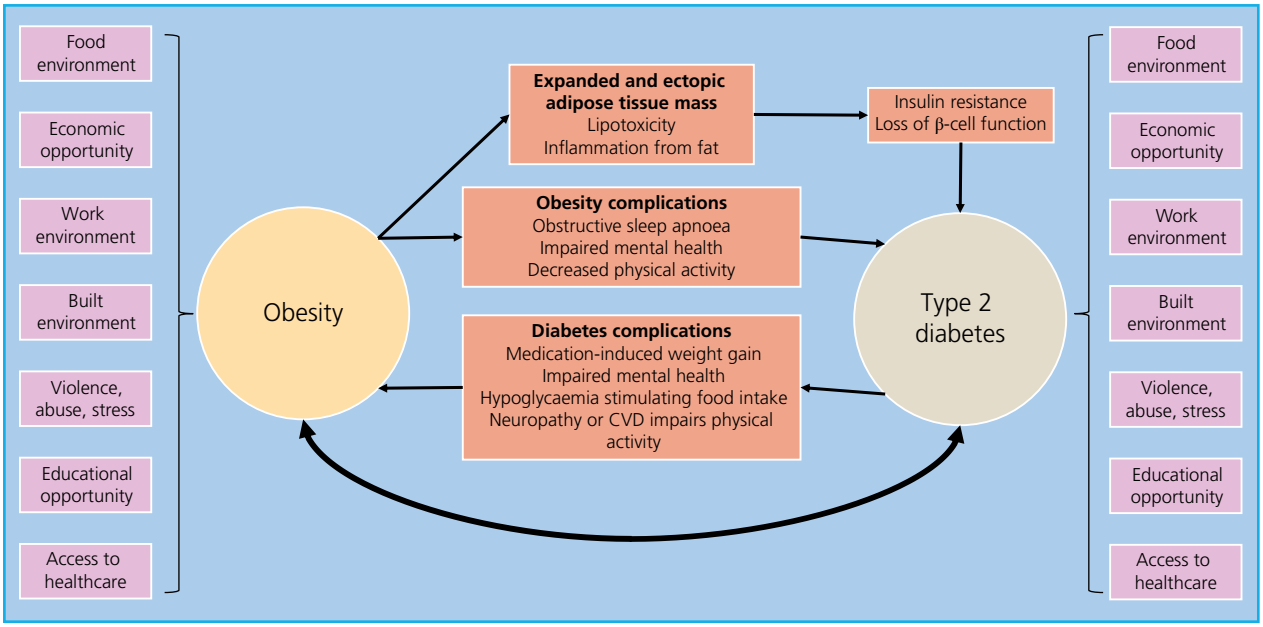

Figure 18.2 Pathways linking the syndemic of obesity and type 2 diabetes. CVD, cardiovascular disease.

Table 18.4 Genetic obesity syndromes.

Obesity syndrome	Gene name	Main distinguishing features
Monogenic		
Leptin deficiency	*LEP*	Severe hyperphagia, hypogonadism, impaired immunity, undetectable serum leptin
Leptin receptor mutation	*LEPR*	Severe hyperphagia, hypogonadism, very high serum leptin
MC4R deficiency	*MC4R*	Accelerated growth, increased final height
POMC deficiency	*POMC*	Hypopigmentation, isolated ACTH deficiency
Prohormone convertase	*PCSK1*	Glucocorticoid deficiency, postprandial hypoglycaemia, hypogonadism, elevated plasma proinsulin and split proinsulin
BDNF deficiency	*BDNF*	Developmental delay, hyperactivity, impaired memory, impaired pain sensation
TrkB deficiency	*NTRK2*	Developmental delay, hyperactivity, impaired memory, impaired pain sensation
Polygenic		
Bardet-Biedl syndrome	*BBS1–16*	Polydactyly, retinal dystrophy, hypogonadism, renal abnormalities
Alström syndrome	*ALMS1*	Progressive loss of vision and hearing, dilated cardiomyopathy, type 2 diabetes, short stature
Prader-Willi syndrome	*15q11–13*	Hypotonia, learning disability, short stature, hypogonadism, severe hyperphagia
Down's syndrome	*Trisomy 21*	Learning disability, short stature, heart disease, moderate obesity from infancy
Polymorphisms (include)	*FTO, MC4R, TMEM18*	In children 0.5 SDS increase in highest vs lowest risk
	GNPDA2, KCTD15, NEGR1	In adults risk scores based on 11–30 susceptibility genes account for twofold risk of obesity
	BDNF, ETV5, SEC16B	Increased risk of obesity; individuals with ≥13 or more obesity-predisposing alleles across
	SH2B1, MTCH2	eight loci were on average 1.46 BMI units (equivalent to 3.7–4.7 kg for an adult of average height) heavier than those individuals with ≤3 alleles

ACTH, adrenocorticotropic hormone; BDNF, brain-derived neurotrophic factor; MC4R, melanocortin 4 receptor; POMC, proopiomelanocortin; SDS, standard deviation score; TrkB, tyrosine receptor kinase B.

cells (liver, skeletal muscle, and adipose tissue) [50]. Measures of insulin resistance such as the homeostatic model assessment of insulin resistance (HOMA-IR) correlate with visceral fat mass, total fat mass, BMI, and waist circumference, but to a much lesser extent with subcutaneous fat, highlighting the importance of adipose distribution [51]. This interplay between obesity and diabetes is further emphasized by the impact of accumulated adipose tissue on insulin resistance that drives cardiometabolic disease progression towards type 2 diabetes, NAFLD, and cardiovascular disease [52]. The bidirectional contribution of NAFLD to both type 2 diabetes and obesity is also well established [50]. However, there exists a wide variation in insulin resistance and β-cell dysfunction and inflammation within the current diabetes classification. This heterogeneity relates to the effects of epigenetic, genetic, environmental, and lifestyle factors on the disease and its progression and complications. Attempts to increase the precision of diagnosis suggest six subtypes of diabetes, of which two are associated with a high BMI [53,54]. Severe insulin-resistant diabetes is characterized by late onset, high BMI, most insulin resistant, highest liver fat content, fatty liver index, NAFLD fibrosis score, and prevalence of NAFLD. Severe insulin-resistant diabetes has the highest risk for macroalbuminuria, chronic renal disease, and ischaemic heart disease and stroke. By contrast, a

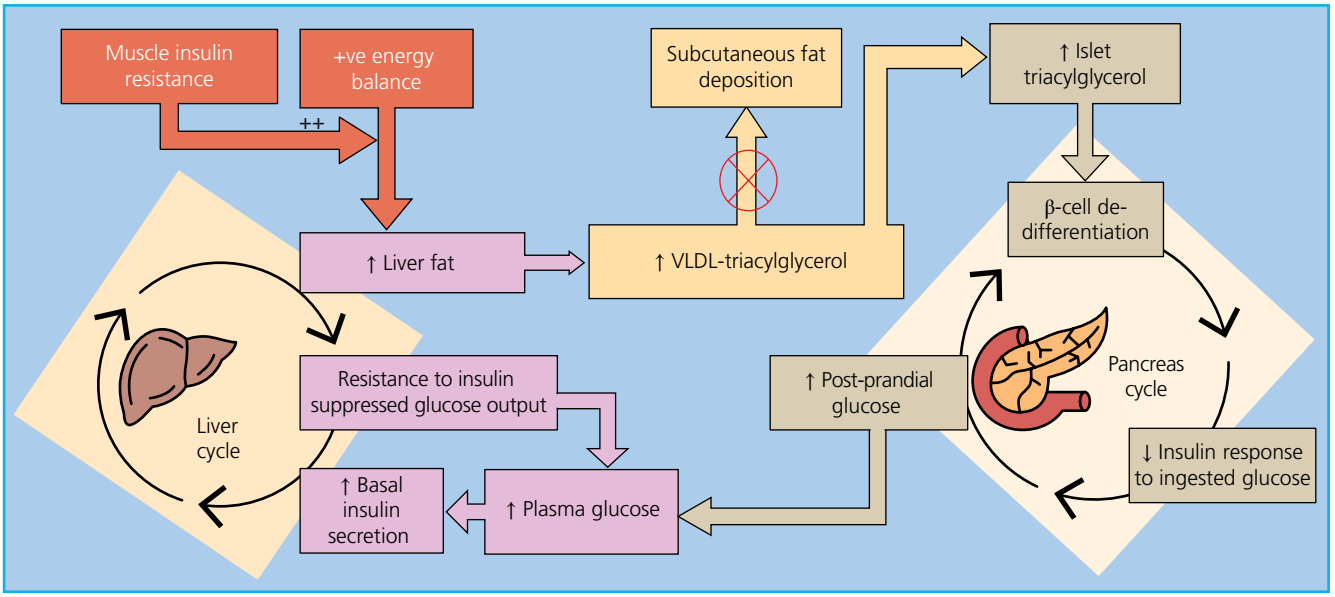

Figure 18.3 Pathways in the twin cycle hypothesis. VLDL, very low-density lipoprotein.

subgroup characterized by a more benign course of their disease is termed mild obesity-related diabetes, with high BMI, early-onset diabetes with intermediate insulin resistance and an intermediate prevalence and risk of diabetes-related complications.

A model (the twin-cycle model) links obesity to the development of type 2 diabetes and explains how weight loss can reverse the process (Figure 18.3) [55]. The model describes how a positive energy balance promotes the deposition of fat in the liver by a process promoted by insulin. The presence of elevated insulin levels drives liver fat accumulation, resulting in decreased hepatic insulin sensitivity, which impairs insulin suppression of hepatic glucose output. This leads to both an increase in blood glucose levels and basal insulin secretion, forming the first vicious cycle. The second vicious cycle results from a spillover of liver-derived triglyceride-rich, very low-density lipoprotein (VLDL). Once subcutaneous fat stores are replete, this drives ectopic fat deposition in other tissues and exposes pancreatic β cells to triacylglycerol accumulation. Since pancreatic β cells are particularly susceptible to fatty acids, this impairs the function and response to post-meal glucose, which combine to elevate blood glucose levels and further impair glucose homeostasis. The resulting chronic hyperglycaemia increases insulin secretion, which results in increased fat deposition in the liver and increased hepatic lipogenesis, so driving both cycles faster. Once these effects on β cells reach a certain threshold, β-cell decompensation occurs, with the onset of clinically overt type 2 diabetes.

It has long been known that these effects are readily reversible, particularly in early type 2 diabetes [56]. Both negative energy balance from energy restriction [57–59] and weight loss [60] can improve insulin resistance and hyperglycaemia, and this has led to a reawakening of interest in the role of therapeutic weight loss in the management of type 2 diabetes.

Treatment

Since obesity is the primary driver for the development of type 2 diabetes, it is unsurprising that therapeutic weight loss is a powerful intervention that can ameliorate or reverse many of the metabolic abnormalities present in those with diabetes. However, this therapeutic approach was largely discredited by the UK Prospective Diabetes Study (UKPDS), which reported in the 1990s that its findings 'confirm(ed) the value of dieting, but in view of the large weight loss and equivalent large reduction in energy intake required in most patients, it is not surprising that few patients achieve near-normal fasting plasma glucose concentrations by diet alone' [61,62].

The metabolic impact of weight loss was shown in an elegant study in which experimental individuals (without diabetes) underwent stepwise periods of weight reduction and weight stabilization. A 5% weight loss did not affect oral glucose tolerance or other measures of glycaemia, but improved organ-specific insulin sensitivity in adipose tissue, liver, and skeletal muscle when assessed by clamp studies [63]. Insulin-mediated suppression of hepatic glucose production and adipose tissue lipolytic activity were maximal after 5% weight loss, whereas insulin-stimulated muscle glucose uptake increased further with greater amounts of weight loss of 11–16%. Greater loss beyond 5% further improved β-cell function, intrahepatic triglyceride content, and adipose tissue expression of genes involved in cholesterol flux, lipid synthesis, extracellular matrix remodelling, and oxidative stress. The impact of the Cuban economic collapse from 1991 to 1995 provided real-world evidence for the impact of energy restriction on weight loss and diabetes: the combination of food shortages and unavoidable increases in physical activity put the entire population in a negative energy balance of at least 20%, with a population-wide average weight loss of 5.5 kg that was associated with rapid declines in diabetes – a 53% fall in incidence at the lowest point [64].

However, despite this knowledge, over the past decades the development of a multiplicity of glucose-lowering drugs, together with potent drugs to manage blood pressure and lipids, has tended to marginalize weight loss as a therapy for diabetes. A recent UK survey found that between 2002 and 2016 there had been a steady increase in the number of people with type 2 diabetes treated with medications (from 39.6% to 56.3%), but that in 2016 fewer than 1 in 4 people with type 2 diabetes received weight management support or referral. The proportion receiving weight management was similar for those with either overweight or obesity [65]. More recently

there has been a revival of interest in developing intensive weight loss regimens with the aim of reversing or remitting type 2 diabetes.

Diabetes reversal and remission

The concept that diabetes could be cured, remitted, or reversed with weight loss was given impetus by a provocatively titled paper: 'Who would have thought it? An operation proves to be the most effective therapy for adult-onset obesity' [66]. Increasing publications on the effects of bariatric surgeries on type 2 diabetes were hampered by a lack of consensus as to what was meant by *cure* or *remission*. The American Diabetes Association (ADA) noted that 'distinction between successful treatment and cure is blurred in the case of diabetes. Presumably improved or normalised glycemia must be part of the definition of remission or cure and that it may be more accurate to use the term remission than cure' [67]. The ADA established a consensus group who defined three outcomes:

- Partial remission.
- Complete remission.
- Prolonged remission based on the duration and degree of normalization of blood glucose off anti-diabetes treatment.

A reconvened consensus group in 2022, representing the European Association for the Study of Diabetes (EASD), Diabetes UK, and the ADA, expanded on the definition and interpretation of remission according to timing and intervention (Table 18.5) [68]. However, these criteria are not without problems. They reflect a highly glucocentric view of type 2 diabetes. First, the criteria for a *normal* glycated haemoglobin (HbA_{1c}) are not universally agreed, and normalizing HbA_{1c} does not necessarily imply normoglycaemia; for example, after bariatric surgery, wide excursions from hyper- to hypoglycaemia are common [69]. Continuous glucose monitoring has shown that after bariatric surgery, hypoglycaemia affects more than 50% of individuals, increases at increasing time from surgery, and is comparable after gastric bypass and sleeve gastrectomy [70]. The risk of inpatient care for hypoglycaemia following gastric bypass is increased nearly threefold [71]. Another conceptual issue is that individuals who have had bariatric surgery retain the operative altering of nutrient passage through the gastrointestinal system, with the related changes in gut hormone, microbiota, and bile acids, and so effectively have not ceased treatment. Even treatment with diet and lifestyle changes may persist after the acute intervention, such that *remission* is retained while they maintain these changes. Last, there are few data on the impact of remission on the reversal of already established or longer-term development of micro- and macrovascular disease.

Table 18.5 Consensus on requirements that define diabetes remission.

Intervention (remission requires an HbA_{1c} measure immediately prior to intervention)	Interval before testing of HbA_{1c} can reliably evaluate the response	Subsequent measurement of HbA_{1c}
Lifestyle	>6 mo after beginning of intervention and >3 mo after stopping pharmacotherapy	
Pharmacotherapy	>3 mo treatment cessation	>3 mo and <1 yr
Surgery	>3 mo after procedure and >3 mo after stopping pharmacotherapy	

Glycated haemoglobin (HbA_{1c}) below the level currently used for initial diagnosis of diabetes, 6.5% (48 mmol/mol), and remaining at that level for at least 3 mo without continuation of the usual anti-diabetes agents as the main defining measurement. In some circumstances, an estimated A_{1C} (eA_{1c}) or glucose management indicator (GMI) <6.5% can be considered an equivalent criterion.

Very low-energy diets and reversal or remission of diabetes

From the earliest days it was recognized that fasting and weight loss could improve carbohydrate metabolism [72]. In the 1970s protein-sparing modified fasts, which were essentially equivalent to contemporary very low-energy (VLED) or very low-calorie diets (VLCD), were investigated for people with insulin-treated type 2 diabetes [73]. Within 19 days of the diet, insulin could be withdrawn with improvements in blood pressure, lipid abnormalities, carbohydrate metabolism, and cardiorespiratory function, and preservation of lean body mass. While a 2004 Cochrane review found insufficient quality of data to recommend VLCDs over other diets in type 2 diabetes [74], evidence for their benefits continues to emerge [75]. β-cell function in people with type 2 diabetes undergoing VLED treatment improves [76], with falls in fasting plasma insulin and C-peptide levels [77] and improvements in dynamic insulin secretion and overall insulin production, modulation of pulsatility, and improved synchrony [78].

Initial interest in VLEDs, usually in the form of liquid meal replacements, was in their potential as an exploratory interventional tool rather than a clinically appropriate therapeutic diet. However, the acceptability of VLEDs, alone or in combination with anti-obesity medications, has increased over the past 20 years and they can be safely and effectively delivered in primary care [75, 79, 80]. The potential for energy restriction and weight loss to *reverse* type 2 diabetes has recently been evaluated in Counterpoint [81] and Counterbalance [82], a series of studies on type 2 diabetes remission. The Counterpoint study provided proof of concept that normalization of glycaemia was possible through weight loss using a VLED, which showed improvement in hepatic insulin resistance and normalization of β-cell function. The Counterbalance study aimed to assess the effect of a VLED on individuals with longer duration of type 2 diabetes. They found that at eight weeks 87% of individuals with short type 2 diabetes duration (<4 years) experienced remission, versus only 50% of those with longer disease duration (>8 years).

The Diabetes Remission Clinical Trial (DiRECT) assessed whether effective weight management, delivered in the primary care setting, could produce sustained remission of type 2 diabetes [83]. Individuals aged 20–65 years with non-insulin-treated type 2 diabetes, diagnosed within the past six years, and a BMI of 27–45 kg/m^2, were cluster randomized across 49 primary care practices to either an intervention in which anti-diabetes and antihypertensive drugs were withdrawn, and a total diet replacement (825–853 kcal/d formula diet for 3–5 months), stepped food reintroduction (2–8 weeks), and structured support for long-term weight loss maintenance were provided, versus a control group receiving best-practice standard care. At one year 24% of participants in the intervention group and none in the control group achieved weight loss ≥15 kg; diabetes remission (defined as HbA_{1c} less than 6.5% [<48 mmol/mol] after at least two months off all anti-

diabetes medications) was achieved in 46% of participants in the intervention group and 4% in the control group. Remission varied with weight loss in the whole study population. At 24 months, in the intention-to-treat population of 149 participants per group, 17 (11%) receiving the intensive intervention and 3 (2%) in the control group had lost ≥15 kg; 53 (36%) and 5 (3%), respectively, had diabetes remission [84].

More recently, the Diabetes Intervention Accentuating Diet and Enhancing Metabolism (DIADEM-I) compared an intensive lifestyle intervention that included a VLED with usual medical care on weight loss and glycaemic outcomes in individuals from the Middle East and North Africa region with type 2 diabetes, aged 18–50 years, a short diabetes duration of less than three years, and a BMI of ≥27.0 kg/m^2. After one year the intensive intervention group achieved a mean 11.98 kg weight loss, with 61% obtaining diabetes remission, compared to a 3.98 kg loss and 12% remission in the control group [85]. The Doctor Referral of Overweight People to Low Energy total diet replacement Treatment Trial (DROPLET) included participants with a BMI ≥30 kg/m^2 (15% of whom had type 2 diabetes) and compared weekly behavioural support for 12 weeks and monthly support for three months with a commercial VLED providing 810 kcal/d (3389 kJ/d) as the sole food during the first eight weeks, followed by reintroduction of food with usual care from a practice nurse and a diet programme with modest energy restriction [86]. Mean weight change at 12 months was −10.7 kg in the VLED group and −3.1 kg in the usual care group, with greater reductions in HbA_{1c} (adjusted difference −2.2 mmol/mol, 95% confidence interval [CI] −4.4 to 0.0 mmol/mol; p = 0.05). Based on these results, the NHS Low Calorie Diet Programme is piloting a low-calorie, total diet-replacement programme for people who are overweight and living with type 2 diabetes [87].

Anti-obesity medications

The development of anti-obesity medications has been hampered until recently by drugs that were of modest weight loss efficacy, and many of which proved to have serious unwanted effects [88–91]. Currently, compared to treatment options for hypertension or type 2 diabetes, few anti-obesity medications are available, but as the physiology of energy balance is increasingly elucidated, many new druggable targets for weight loss have reawakened the search for effective and safe therapies [92].

The development of glucagon-like (GLP-1) receptor agonists, already well established as treatments for type 2 diabetes, as well as dual agonists that combine GLP-1 and glucose-dependent insulinotropic peptide (GIP) agonism, has, and is, transforming the potential for anti-obesity medications not only to produce double-digit weight loss (i.e. ≥10%) but to prevent and reverse type 2 diabetes (Table 18.6). Central GLP-1 is a physiological regulator of food intake acting on both appetite and reward-related brain areas [103], while GIP appears to activate neurons distinct from GLP-1, to inhibit food intake in a manner that is additive to GLP-1 [104]. The main unwanted effects of this class of drugs, which have been seen across all clinical trials, are gastrointestinal with mild to moderate nausea and vomiting when treatment is initiated. These side effects can be limited by slow dosage escalation. An increase in gallstones appears not to be fully accounted by weight loss and can rarely lead to pancreatitis.

Liraglutide underwent evaluation as an anti-obesity medication in the Satiety and Clinical Adiposity Liraglutide Evidence in Nondiabetic and Diabetic Individuals (SCALE) programme [105]. Four pivotal trials (the design of which informed the clinical evaluation of both semaglutide and tirzepatide) included a 56-week trial of 3731 individuals without type 2 diabetes and a BMI ≥30 kg/m^2 or ≥27 kg/m^2 with an obesity complication. Weight loss was significantly greater with liraglutide compared to placebo (estimated treatment difference −5.6 kg; 95% CI −6.0 to −5.1; p < 0.001) and more individuals achieved ≥5% of their body weight. There were also significantly greater reductions in blood pressure, total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, fasting glucose, fasting insulin, and HbA_{1c} with liraglutide compared to placebo. The other trials evaluated efficacy in individuals with obesity and sleep apnoea, type 2 diabetes, and for weight maintenance after an initial intensive diet. A *post hoc* analysis confirms cardiovascular safety and suggests possible benefit [106] in keeping with evidence of liraglutide (and semaglutide) at a lower dose indicated for type 2 diabetes [107].

Semaglutide is a human GLP-1 analogue with 94% structural homology with native human GLP-1. An amino acid substitution at position 8 makes semaglutide less susceptible to degradation by dipeptidyl peptidase-4, and acylation of the peptide backbone with a spacer and C-18 fatty di-acid chain allows specific binding to albumin giving a half-life of approximately one week, to allow once-weekly administration [108]. Extensively evaluated as a treatment for type 2 diabetes, the Semaglutide Treatment Effect in People with Obesity (STEP) clinical trial programme has investigated higher doses (2.4 mg weekly by subcutaneous injection) in combination with diet and lifestyle advice, in overweight and obesity [109]. In the pivotal STEP 1 trial [110], weight loss after 68 weeks was 14.9% in those on semaglutide compared to 2.4% on placebo. For the trial product estimand (the effect if the drug or placebo was taken as intended), the corresponding changes were −16.9% and −2.4% (estimated treatment difference −14.4%; 95% CI −15.3 to −13.5). One third of individuals lost ≥20% of their initial weight on semaglutide compared to 1.7% receiving placebo. Semaglutide produced highly clinically significantly greater reductions in waist circumference and cardiometabolic risk factors. The STEP trials included individuals with pre-diabetes, but not type 2 diabetes who were studied in STEP 2 [102]. The glycaemic effects are shown in Table 18.6. The results of the Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity (SELECT) cardiovascular outcome trial in people with overweight and obesity (but not type 2 diabetes) are awaited [111].

Tirzepatide is a dual GIP and GLP-1 receptor agonist developed for the treatment of type 2 diabetes, obesity, and non-alcoholic steatohepatitis. Evaluated and approved for the treatment of type 2 diabetes, the SURMOUNT-1 trial has reported efficacy and safety of tirzepatide 5, 10 and 15 mg weekly by subcutaneous injection, in adults with obesity or overweight who did not have diabetes [112]. After 72 weeks, the mean weight loss was 15.0% with 5 mg weekly doses of tirzepatide, 19.5% with 10 mg, and 20.9% with 15 mg doses compared to 3.1% with placebo. A loss of ≥20% was achieved by 57% of those on the highest dose, and over one-third lost ≥25%; waist circumference reduced by 20 cm. Nearly all with pre-diabetes at baseline reverted to normoglycaemia. All pre-specified cardiometabolic measures improved including blood pressure, fasting insulin, and lipids.

Setmelanotide, a melanocortin-4 receptor agonist, has been developed for use in individuals with severe obesity due to either proopiomelanocortin, proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor deficiency [113]. While many of these syndromic obesities are associated with the development of type 2

Table 18.6 Headline results of trials exploring the effect of anti-obesity medications in people with pre-diabetes and diabetes.

Medication name	Mode of action	Weight loss–independent effects on diabetes	Impact on individuals with pre-diabetes	Impact on individuals with diabetes
Orlistat	Lipase inhibitor	No	XENDOS [93] Weight loss kg: 5.8 vs 3.0 Conversion rate to type 2 diabetes (%): 18.8 vs 28.8 (RR reduction = 45%) Pooled clinical trial data [94] Weight loss kg: 6.72 vs 3.79 Conversion rate to type 2 diabetes (%): 3.0 vs 7.6	Meta-analysis of 7 trials [95] Weight loss kg: 3.8 vs 1.4 HbA_{1c} (%): −0.69 vs −0.27 HbA_{1c} (mmol/mol): −7 vs −3
Phentermine 15 mg + topiramate 92 mg	Centrally acting anorectic	No	?	OB-202/DM-230 [96] Weight loss (%): 9.4 vs 2.7 HbA_{1c} (%): −1.6 vs −1.2 HbA_{1c} (mmol/mol): −17 vs −13 CONQUER [97] Weight loss (%): −8.8 vs −1.9 HbA_{1c} (%): −0.4 vs −0.1 HbA_{1c} (mmol/mol): 5 vs 1
Bupropion SR + naltrexone SR	Centrally acting anorectic	No	?	COR-DM [98] Weight loss (%): 5.0 vs 1.8 HbA_{1c} (%): −0.6% vs −0.1% HbA_{1c} (mmol/mol): 6 vs 1
Liraglutide 3.0 mg daily SC	GLP1-RA	Yes	SCALE Prediabetes [99] Weight loss at week 160 (%): 6.1 vs 1.9% Conversion rate to type 2 diabetes: 2.7 times longer with liraglutide; hazard ratio 0.21	SCALE Diabetes: 3.0 mg vs 1.8 mg vs placebo [100] Weight loss (%): 6.0 vs 4.7 vs 2.0 HbA_{1c} (%): −1.3 vs −1.1 vs −0.3 HbA_{1c} (mmol/mol): −14 vs −12 vs −3 HbA_{1c} ≤6.5% (48 mmol/mol; %): 56.5 vs 45.6 vs 15
Semaglutide 2.4 mg weekly SC	GLP1-RA	Yes	STEP 1 [101]: Pre-diabetes conversion to normoglycaemia Semaglutide: 45.4% baseline vs 15.3% at week 68 Placebo: 40.2% baseline, 49.1% at week 68 Estimated treatment difference: HbA_{1c} −0.35% (−4 mmol/mol) STEP 3 [101] Semaglutide: 48.2% baseline vs 10.5% at week 68 Placebo: 52.9% baseline, 44.0% at week 68 Estimated treatment difference: HbA_{1c} −0.29% (3 mmol/mol) STEP 4 [101] Semaglutide: 49.0% baseline vs 10.2% at week 68 Placebo: 42.5% baseline, 28.7% at week 68 Estimated treatment difference: HbA_{1c} −0.3% (3 mmol/mol)	STEP 2 : 2.4 mg vs 1.0 mg vs placebo [102] Weight loss (%): 9.6 vs 7.0 vs 3.4 HbA_{1c} (%): −1.6 vs −1.5 vs −0.4 HbA_{1c} (mmol/mol): −17 vs −16 vs −4 HbA_{1c} ≤6.5% (48 mmol/mol; %): 67.5 vs 60.1 vs 15.5
Tirzepatide[a]	GLP1-GIP co-agonist	Yes	'95.3% of the participants with prediabetes at baseline in the tirzepatide groups had reverted to normoglycemia vs. 61.9% on placebo'	
Setmelanotide	MC4RA	No	Not assessed	Not assessed

[a] Not currently approved for treatment.
GIP, glucose-dependent insulinotropic peptide; GLP1-RA, glucagon-like peptide 1 receptor agonist; HbA_{1c}, glycated haemoglobin; MC4RA, melanocortin-4 receptor agonist; RR, relative risk; SC, subcutaneously; SR, sustained release.

diabetes, the trials did not show statistical glycaemic improvement, but were small and underpowered [114, 115].

Many promising new anti-obesity medications (both novel compounds and combinations such as amylin analogues and GIP + glucagon + GLP-1 tri-agonists) are in clinical development and promise greater weight loss efficacy and/or precision medicine [92].

Bariatric surgery

Bariatric surgery with gastric bypass or sleeve gastrectomy improves glycaemia through a variety of mechanisms other than weight loss alone (Chapter 38). Caloric restriction drives early improved glycaemic homeostasis, but the anatomical alterations of the gut and intestines lead to more rapid delivery of undigested food to the small intestine with subsequent increased release of the gut-derived GLP-1. Exclusion of duodenal nutrient exposure is postulated to produce weight loss–independent effects on glucose homeostasis. Additionally, changes in the gut microbiota may contribute [116]. The Swedish Obese Subjects (SOS) study first showed that 10 years after a variety (some now obsolete) of procedures, mean weight loss of 16.1% was associated with both recovery from (36% vs 13% in controls) and reduction in the incidence of (7% vs 24% in controls) type 2 diabetes [117]. Bariatric surgery is an effective way of obtaining weight loss and improving intermediate glycaemic outcomes in people with type 2 diabetes and obesity class 1 [118, 119]. Recent studies comparing surgery to conventional diabetes treatment suggest that better glycaemic levels can be achieved with surgery, with a substantial proportion of individuals developing prolonged remission from diabetes. A systematic review of the remission rate of type 2 diabetes after gastric bypass and sleeve gastrectomy found that at one year it was higher among those undergoing gastric bypass, at 57%, and 47% of those with sleeve gastrectomy achieved remission. After 2–5 years' follow-up, the remission rate was 50% and 46%, respectively [120]. Many models have been developed and proposed to predict diabetes remission after surgery [121], two of which are well validated with acceptable to excellent discrimination [122]. Whether surgery can or will ever be scaled up sufficiently to meet clinical need, or could be (partially) displaced by new anti-obesity medications that produce nearly equivalent weight losses, remains to be seen.

Management of obesity in type 1 diabetes

A growing problem is the increasing prevalence of obesity in individuals with type 1 diabetes in whom absolute insulin deficiency coexists with insulin resistance due to adiposity, so-called *double diabetes*. The consequences of overweight or obesity in people with type 1 diabetes are worrisome, as diabetes-related and obesity-related complications, including cardiovascular disease, stroke, and various types of cancer, are increased [123]. In one clinic, 64% had a BMI of >25 kg/m^2 and 25% had a BMI of ≥30 kg/m^2 [124], while a type 1 diabetes registry in the USA found that 29% of adults had overweight and 20% obesity [125]. It is postulated that over and above the factors driving weight gain in the general population, in those with type 1 diabetes insulin-intensive therapies, hypoglycaemia avoidance strategies, and possibly changes in growth hormone could exacerbate the difficulties of weight control [123]. While all approaches to treating obesity in people with type 2 diabetes could be applied to those with type 1 diabetes, there is much less evidence on which to assess efficacy and, importantly, safety.

Convergence of obesity and diabetes treatments

Interventions initially designed to treat obesity are increasingly being considered as primary treatment of type 2 diabetes (e.g. bariatric surgery) and, conversely, anti-obesity medications initially developed for type 2 diabetes are (often at higher doses) highly effective medications. Many people living with type 2 diabetes are not on guideline-directed weight loss therapy and a survey found that among 2910 adults with type 2 diabetes who qualified for anti-obesity treatment, only 40 participants (2.2%) were on an anti-obesity medications within 30 days of survey interview [126]. Furthermore, weight loss goals may be compromised by the fact that up to 66% of individuals are receiving weight-inducing anti-diabetes therapy. The now substantial evidence of the impact of weight loss on type 2 diabetes (and many other obesity complications), readily achievable by intensive dietary and lifestyle interventions, anti-obesity medications, or bariatric surgery, should make weight loss a principal, if not primary, goal for the management of type 2 diabetes [127]. Substantial barriers remain. Few healthcare providers reimburse obesity treatment. Even when treatment costs are covered, implicit rationing is commonplace, either of access to bariatric surgery or continued treatment with anti-obesity medications [128]. In the UK, the National Institute for Health and Care Excellence (NICE) recommends an expedited assessment for people with a BMI ≥35 kg/m^2 with onset of type 2 diabetes in the past 10 years, assessment for people with a BMI of 30.0–34.9 kg/m^2 with the onset of type 2 diabetes within 10 years, and people of Asian origin with the onset of type 2 diabetes at a lower BMI than other populations [129], yet rates of surgery meet less than 1% of need [130]. Although both obesity and diabetes management guidelines are evolving to recognize the importance of weight management as pivotal to good diabetes care, prejudice and ignorance about treating obesity remain common. In one study of primary care providers randomly assigned to evaluate the records of individuals with either obesity or normal weight, providers who evaluated those with obesity were more likely to rate the encounter as a waste of time and indicated that they would spend 28% less time with the individual with diabetes compared with those who evaluated normal-weight individuals [131, 132]. Endocrinologists are not immune from these views and attitudes [133].

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19 The Microbiome and Diabetes

Amanda J. Cox[1,2], Nicholas P. West[1,2], and Allan W. Cripps[1,3]

[1] Menzies Health Institute Queensland, Griffith University, Southport, QLD, Australia
[2] School of Pharmacy and Medical Sciences, Griffith University, Southport, QLD, Australia
[3] School of Medicine, Griffith University, Southport, QLD, Australia

Key points

- The intestinal microbiome is a diverse collection of over 1000 bacterial species that are increasingly recognized as playing critical roles in host function and subsequently health and disease.
- A range of lifestyle and environmental factors, including diet, medication, and hygiene, have been shown to influence the composition of the intestinal microbiome and associations between the microbial composition and both body mass and type 2 diabetes have been reported.
- The intestinal microbiome can influence intestinal permeability and thereby play a regulatory role in the development of metabolic endotoxaemia.
- Metabolic endotoxaemia has the potential to activate immune pathways that interface with insulin signalling pathways and can affect glycaemic levels.
- Microbial metabolites can act locally at the intestinal mucosa to regulate enteroendocrine cell function, incretin signalling, and subsequently glycaemic levels.
- The intestinal microbiome can modulate composition of the bile acid pool and downstream signalling pathways, including farnesoid X receptor (FXR) and G-protein–coupled bile acid receptor (TGR5), to influence glycaemic levels.
- The intestinal microbiota may also contribute to the risk for type 1 diabetes; inappropriate immune education by the microbiota may potentiate autoimmune destruction of pancreatic β cells in genetically susceptible individuals.

The microbiome

The human body is inhabited by a diverse and populous array of microorganisms, termed the microbiome, including bacteria, viruses, fungi, and archaea. The genetic material from this collection of microbes, termed the metagenome, is now estimated to be 150 times larger than that of the human genome [1]. The gastrointestinal tract contains the majority of commensal microbes; however, the urogenital tract, skin, and oral cavity provide niche environments for additional species [2]. Microbes colonize the sterile gastrointestinal tract during birth and are implicated in early-life programming of the immune and metabolic systems, protection from infection, and the synthesis of vitamins, minerals, and fatty acids, which continues throughout the lifespan of an individual [3]. Given its size, diversity of physiological functions, and interactions with other organ systems, the microbiome can be considered as an organ in its own right.

Revised estimates suggest close to 2000 different bacterial species may persist in the gut [1], with the number of bacterial cells exceeding 10^{13} and being as numerous as the total number of host cells in the body [4]. Given the dominance of anaerobic species, early attempts to characterize the diversity of the intestinal microbiome were limited by available sample collection methods and culture techniques [5]. Advances in molecular biology techniques, including use of deep- and next-generation sequencing, have facilitated several large-scale projects, including the European MetaHIT Project [6] and the National Institutes of Health Human Microbiome Project [7], which have provided additional insights into the diversity of the commensal species. Initially these projects classified 90% of gut bacteria as belonging to either one of two phyla, namely Bacteroides or Firmicutes. Within these two divisions three enterotypes were defined based on variation in either *Bacteroidetes* (enterotype 1), *Prevotella* (enterotype 2), or *Ruminococcus* (enterotype 3) that appeared stable across continents [8, 9]. Classification of stable enterotypes is now considered oversimplified, with the abundance of resident species along the gastrointestinal tract alone displaying up to 90% diversity between individuals in similar geographical locations and thought to be shaped by age, hygiene, medication use, and diet [10].

The microbial species resident in the gastrointestinal tract are increasingly recognized as playing critical roles in host function and subsequently health and disease [11–13]. The synergistic relationship between the intestinal microbiota and host provide several benefits to the host, including (i) resistance to infection by pathogenic microorganisms through direct competition for nutrients and attachment sites and production of antimicrobial substances; (ii) promotion of epithelial cell proliferation and differentiation to maintain an intact mucosal surface; (iii) promotion of the development of the gut-associated lymphoid tissue via initiation of dendritic cell maturation and B- and T-lymphocyte differentiation; and (iv) energy harvest from non-digestible dietary starches [14–18] (Figure 19.1).

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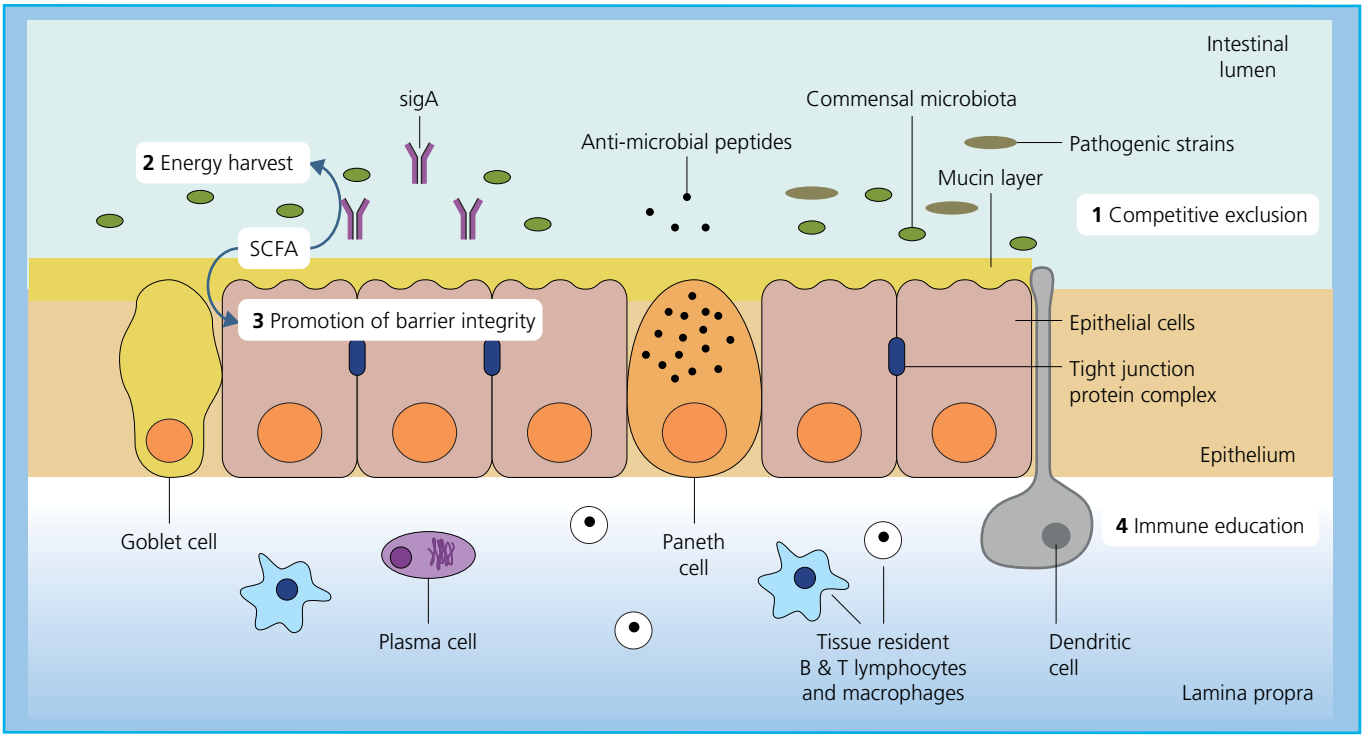

Figure 19.1 A synergistic relationship between the intestinal microbiome and post provides a number of benefits, including (1) competitive exclusion of pathogenic strains; (2) energy harvest; (3) promotion of barrier integrity; and (4) immune education. SCFA, short-chain fatty acids. Source: Modified from Cox et al. 2014 [11].

Bacterial fermentation of non-digestible dietary starch occurs predominantly in the colon [19] and produces short-chain fatty acids (SCFAs; primarily acetate, propionate, and butyrate), which have received particular attention as mediating the beneficial effects provided by the intestinal microbiome. Butyrate in particular is recognized as the main energy source for colonic epithelial cells, and is thought to stimulate blood flow and the secretion of gut hormones, enhance fluid and electrolyte uptake, and increase mucin release, all of which contribute to a local tropic effect, epithelial cell proliferation and differentiation, and maintaining integrity of the intestinal mucosa [20–22]. The application of '-omics' technologies has further broadened knowledge of the roles of the commensal microbial species in host function, with bacterial communities identified with specific roles in regulating biochemical and metabolic pathways [23, 24].

Greater understanding of the role of the microbiota in regulating metabolic function and immune homeostasis has also led to a growing focus on the contribution of the microbiota to risk for diabetes. The composition of the microbiota is altered in obesity and may promote increased extraction of energy from food, altered intestinal permeability, and upregulation of inflammatory signalling. Links between the microbiota and the biochemical processes underpinning the onset and progression of diabetes offer promise that microbial manipulation may be a strategy to reduce the growing burden of associated disease. This chapter will explore the ways in which the intestinal microbiota contribute to diabetes by promoting the accumulation of adipose tissue and altering metabolic and immune homeostasis.

The intestinal microbiome is associated with body mass

Given the documented relationship between excess body mass and risk for type 2 diabetes, links between the intestinal microbiome and excess body mass are of interest when considering the role of the microbiome in diabetes pathogenesis. In animal models, lower body mass and body fat in germ-free mice compared to wild-type counterparts [25], even following exposure to a high-fat and sugar-rich Western-style diet [26], suggest that the absence of microbial colonization in the gastrointestinal tract impairs energy harvest. Studies involving transplantation of the intestinal microbiota further implicate the microbiome as a contributor to excess body mass; transplantation of wild-type microbiota to germ-free mice normalizes body weight between groups [25], while transplantation of microbiota from obese mice results in an increase in fat mass in germ-free animals [27]. Research examining the transplantation of microbiota from obese or lean human donors into germ-free mice is mixed. One investigation has reported greater weight gain over 50 days in recipient animals receiving obesity-associated microbiota [28]. However, a comparison of three diets including a control diet, Western diet, or 45% high-fat diet in mice with gut microbiota from lean or obese human donors found that after 22 weeks, final body weight or body composition of animals did not significantly differ based on source of human-donor material (lean or obese) [29]. Collectively, these data suggest that particular microbiome profiles may favour accumulation of excess body weight, itself a risk factor for type 2 diabetes.

In humans, direct comparison of the composition of the intestinal microbiota between individuals with overweight and lean individuals has produced mixed findings, likely to be the result of modest sample sizes examined in early studies and inherent variability between individuals in response to other environmental factors [30], in addition to host genetics [31]. A significant decrease in the relative abundance of Bacteroidetes, but an increase in Firmicutes in individuals with obesity, has been reported [32]. Similarly, reductions in overall bacterial diversity [33, 34] and reductions in relative abundance of Bacteroidetes, increased relative abundance of Actinobacteria, but no significant change in Firmicutes between individuals

with obesity and lean individuals have also been observed [34]. However, others report no difference in the dominant phyla [35, 36], and an increased relative abundance of Bacteroidetes in individuals with obesity compared to lean individuals [37]. While these inconsistencies are increasingly acknowledged [38], these studies have revealed that the intestinal microbiota is not static and that the composition of the microbiome can vary both within and between populations.

Dietary intervention studies further support the dynamic nature of the intestinal microbiome. Increased caloric content (2400 or 3400 kcal/d at similar macronutrient profiles; 24% protein, 16% fat, and 60% carbohydrates) in otherwise healthy humans for as little as three days has been reported to increase the abundance of Firmicutes and decrease the abundance of Bacteroidetes [35]. Even more acute changes have been suggested, with a subsequent study in otherwise healthy adults noting changes in the composition of the intestinal microbiota within 24 hours of initiation of a high-fat diet [39]. Changes in the intestinal microbiota in response to weight-reducing diets have also been reported, including reduction in the abundance of some specific Firmicutes species following a four-week low-carbohydrate weight-reducing diet in men with obesity [36] and a decreased relative abundance of Bacteroidetes in men with obesity following a four-week high-protein low-carbohydrate diet [40]. It remains to be determined if alterations in the intestinal microbiota that promote energy harvest are a cause or a consequence of Western diets and excess body mass. However, given the functions of the intestinal microbiota beyond energy harvest, additional mechanisms may also contribute to the risk for obesity and associated disease.

Composition of the intestinal microbiome is altered in type 2 diabetes

Potential contributions of the gut microbiota to the pathogenesis of metabolic syndrome and type 2 diabetes are increasingly recognized [41–44]. Comparison of intestinal microbial composition between individuals with and without type 2 diabetes has traditionally relied on 16s rRNA characterization. Conflicting outcomes in terms of overall microbial diversity are noted; some groups report no difference in overall microbial diversity between individuals with type 2 diabetes and controls [45, 46], while others suggest a decrease in microbial diversity in people with type 2 diabetes [47–49]. Despite the discrepancies relating to microbial diversity, the majority of studies report differences in the relative abundance of specific microbial taxa between people with and without type 2 diabetes [45, 50–52], including decreased relative abundance of specific Bacteroidetes species, such as Bifidobacteria [46, 53] and Bacteroides [47, 54]. The modest sample sizes (groups from 8 to 64 individuals) employed in some of the earlier studies and the degree of species identification possible using 16s rRNA methodologies are recognized limitations in the field and have limited the wider application of such observations.

However, the adoption of full metagenome sequencing methodologies in response to reduced costs has provided greater insights into altered microbial composition in type 2 diabetes. Notable studies include those performed in an ethnic Chinese type 2 diabetes case–control cohort (n = 345) in a two-stage design [55]; in a cohort of almost 3000 European women classified into those with type 2 diabetes, impaired glucose tolerance, or normal glucose metabolism [56]; in a cohort of people with treatment-naïve type 2 diabetes, prediabetes, and normal glucose tolerance (n = 254) [57]; and a multiethnic cohort (n = 784) with stratification of individuals with type 2 diabetes based on metformin treatment [58]. All studies report differences in the abundance of specific bacterial taxa in individuals with type 2 diabetes compared to those without diabetes. Consistent observations include enrichment of opportunistic pathogens, including Eggerthella species and *Escherichia coli* [55, 57], as well as Lactobacillus species [56, 58] and depletion of known butyrate producers including *Faecalibacterium prasnitzii*, Roseburia species, and Eubacteria species [55–58] in individuals with type 2 diabetes relative to controls. Beyond microbial composition, metagenome analysis allows for inferences of potential collective microbial function. For the studies mentioned, and consistent with the compositional observations, decreased potential for butyrate biosynthesis has been noted in individuals with type 2 diabetes [55], along with increased potential for membrane transport of sugars [55, 56] and upregulation of a range of genes involved in oxidative stress pathways [55, 56]. In addition, these studies have been able to use combinations of metagenome markers to successfully predict type 2 diabetes status [55–57], providing further support for the relationships between the gut microbiome and risk of type 2 diabetes.

The intestinal microbiome can influence intestinal permeability

A permeable intestinal mucosa is necessary to facilitate critical absorptive functions, but maintenance of barrier exclusion is essential in isolating the intestinal microbiota within the intestinal lumen. The interaction between various integral membrane proteins and cytoskeletal components provides a structural framework to maintain integrity of the intestinal mucosa via intercellular tight junctions. The intestinal microbiota has been suggested to contribute to the ongoing remodelling of the mucosal epithelium [59, 60] and the direct roles of particular microbial metabolites, including tryptophan metabolites, in regulating mucosal barrier function are also recognized [61, 62]. *In vitro* experiments utilizing cultured intestinal epithelial cells have demonstrated that treatment with commensal and probiotic microbial species [63, 64] or a *Faecalibacterium prasnitzii*–derived protein preparation [65] elicit upregulation and increased phosphorylation of key tight junction proteins and reductions in paracellular permeability. Likewise, colonization of germ-free mice with probiotic species has been shown to result in the upregulation of key tight junction proteins [66] and normalization of intestinal barrier function in animal models of disease [66, 67]. Further, human clinical studies involving manipulation of the intestinal microbiota via probiotic supplementation report outcomes that include increased tight junction protein expression in collected duodenal biopsy samples [68], decreased faecal excretion of the key tight junction protein zonulin [69], and reductions in intestinal permeability assessed using a dual-glucose absorption test [70, 71], all suggesting preserved integrity of the intestinal mucosa mediated by the intestinal microbiota. Conceivably, altered composition of the intestinal microbiota reported in obesity could impact adversely on intestinal permeability and contribute to translocation of the intestinal microbiota to the circulation and subsequent systemic responses that may contribute to an increased risk for type 2 diabetes.

Metabolic endotoxaemia

Regardless of the initiating sequence of events, alterations in intestinal permeability have the potential to trigger metabolic endotoxaemia. Metabolic endotoxaemia describes modest concentrations

of bacterial lipopolysaccharide (LPS) in the systemic circulation in the absence of infectious stimuli [72]. LPS is a cell wall component of Gram-negative bacterial species and the intestinal microbiota represents a significant reservoir for LPS entry into the circulation. The appearance of LPS in the circulation has been proposed to result from passive diffusion across an intestinal mucosa where tight junction integrity has been compromised and intestinal permeability increased [73]. Active transport pathways have also been implicated in metabolic endotoxaemia. LPS has been found to be incorporated in chylomicron fractions [74, 75], suggesting that active absorption across the intestinal mucosa as part of normal digestion and absorption may also account for the appearance of LPS in the circulation.

Indeed, diet has been one factor shown to influence LPS translocation across the intestinal mucosa. A dose-dependent relationship between dietary fat content (40–70% total caloric content over four weeks) and plasma endotoxin levels has been reported in several murine feeding studies [72, 76]. The same murine model has also shown that antibiotic treatment, resulting in a decreased intestinal microbial load, attenuates the increase in plasma LPS concentrations following the four-week high-fat feeding [77] and provides further confirmation that the intestinal microbiota is a critical component of metabolic endotoxemia. Likewise, attenuation of the increase in plasma LPS concentrations following a 14-week high-fat (70%) diet has also been reported in a mouse model where the diet was supplemented with a fermentable dietary fibre [78], thought to preserve the integrity of the intestinal mucosa, further implicating intestinal permeability as a determinant of metabolic endotoxaemia.

An association between dietary composition and metabolic endotoxaemia has also been reported in human studies. Acute increases in plasma LPS have been reported within one [79, 80] to three hours [81] following consumption of a high-fat meal by otherwise healthy volunteers, with elevations persisting for up to five hours post-prandially [82], and greater post-prandial excursions in LPS also reported in individuals who subsequently develop overt type 2 diabetes [83]. Further, dietary fat content was significantly correlated with plasma LPS concentrations in an epidemiological study of 201 healthy middle-aged men [76] and a small feeding study demonstrated that, even among healthy volunteers (n = 8), a month long Western-style (40% fat) diet was associated with significant (~70%) increases in plasma LPS [84]. These data support the potential for dietary habits associated with risk for obesity and obesity-associated disease to also trigger translocation of the intestinal microbial contents to the circulation.

Metabolic endotoxaemia in type 2 diabetes

While the relationships between obesity, diet, and metabolic endotoxaemia have received particular attention, epidemiological data also implicate circulating endotoxin in risk for type 2 diabetes. Higher plasma LPS concentrations have been reported in both adults with impaired fasting glucose relative to healthy controls [85] and those with overt type 2 diabetes [86–88]. In addition, a larger analysis involving the FINRISK97 cohort of ~6600 Finnish adults found that circulating endotoxin concentrations at baseline were significantly higher in the individuals with type 2 diabetes and were predictive of those who developed overt type 2 diabetes over the 10-year follow-up period [89]. Likewise, another prospective study, which quantified total 16s rDNA concentration present in the circulation, as a surrogate of intestinal permeability, at baseline and following nine years of follow-up, found that higher baseline concentrations were predictive of type 2 diabetes development over follow-up [90]. Given these relationships, understanding the physiological responses to increased transit of microbial moieties across the gut mucosa may provide further insight into the pathogenesis of type 2 diabetes.

While the impact of sepsis on glucose metabolism has been established [91, 92], ethical and logistical challenges mean that few studies have directly manipulated plasma LPS and/or the intestinal microbiota as a way to establish causality for type 2 diabetes. However, LPS infusion in a mouse model has been shown to induce changes in insulin sensitivity and glucose levels, supporting a causal role for metabolic endotoxaemia in type 2 diabetes development [72]. Chronic low-dose subcutaneous LPS infusion (300 µg/kg/d) over four weeks elicited increases in fasting glucose and insulin, impaired glucose clearance in response to an oral glucose load, and increased hepatic gluconeogenesis, all suggesting the loss of glycaemic control [72]. In healthy humans, the acute effects of intravenous LPS infusion (20 U/kg ~2 ng/kg total dose) have been assessed during a 10-hour euglycaemic hyperinsulinaemic clamp protocol and significant reductions in glucose utilization were noted [93]. Subsequent studies have also reported decreases in insulin sensitivity and increased insulin resistance in response to low-dose LPS infusion protocols [94, 95], further implicating LPS as a causal factor in the development of insulin resistance.

Modulation of the intestinal microbiome can alter in insulin sensitivity

Beyond these seminal studies implicating bacterial LPS as an initiating factor in impaired glucose metabolism, direct modulation of the intestinal microbiota also affects indices of glucose homeostasis. Use of antibiotic treatment over periods ranging from two to eight weeks in genetically modified phenotypically obese mice (*ob/ob*) [77, 96] and in diet-induced obesity models [97, 98] modulates the gut microbial composition, reduces the level of endotoxaemia, and elicits improvements in indices of glucose metabolism. Further, a growing number of studies also support the potential for probiotic supplements to have positive effects on glucose metabolism. Single-strain probiotic supplements administered over 14 weeks of high-fructose feeding and over eight weeks in a diabetic rat model were associated with lower fasting glucose and insulin and improved glucose clearance following a glucose tolerance test [99], and lower fasting insulin and homeostatic model assessment for insulin resistance (HOMA-IR) [100], respectively. Similarly, in high-fat fed mice, improved glucose clearance after glucose tolerance tests has been reported following Lactobacillus single-strain probiotic supplementation over 5 [101] and 10 weeks [102], and also in response to dual- [103] and multistrain supplements [104]. Collectively, these data support the potential for modulation of the intestinal microbiota to mediate improvements in insulin sensitivity.

Findings from antibiotic studies have yet to be widely replicated in humans in the context of glucose metabolism. A recent meta-analysis assessing the impacts of antibiotics on metabolic status in adults with obesity includes just two placebo-controlled trials, with effects that are largely unclear [105]. The effects of probiotic supplementation have also been assessed in a series of human clinical studies. While not all probiotic supplementation trials have been able to demonstrate definitive benefits on glycaemia [106, 107], early positive findings included improved insulin sensitivity following four weeks of probiotic supplementation in a cohort of adults with overweight (n = 45) and a range of glucose tolerance [108].

In addition, two trials from the same laboratory report reductions in fasting glucose, fasting insulin, and HOMA-IR in a cohort of overweight adults [109] and in otherwise healthy young adults [110] following six weeks of probiotic supplementation. A series of recent meta-analyses also support modest, but beneficial, effects of probiotics on measures of glycaemic metabolism in individuals with type 2 diabetes [111–114]; however, selection of specific strains likely to have the greatest efficacy is unresolved.

The application of faecal microbial transplantation as a further strategy for modulation of the gut microbiota in obesity and metabolic disease is of growing interest [115–117]. However, there remain few human clinical studies assessing indices of metabolic health as primary outcomes. An early study involving men with metabolic syndrome administered either an autologous gut microbiota duodenal infusion (n = 9) or an allogenic gut microbiota duodenal infusion from healthy lean donors (n = 9) and reported improvements in peripheral insulin sensitivity and a trend towards reduced endogenous glucose production six weeks following allogenic infusion only [118]. A subsequent investigation from the same team, also involving men with obesity and metabolic syndrome (n = 38) and utilizing a similar design reported that improvements in peripheral insulin sensitivity observed at 6 weeks were not maintained at 18 weeks, and noted that low baseline microbial diversity was predictive of positive metabolic responses among recipients of faecal microbial transplantation [119].

Microbial metabolites may be key mediators linking the gut microbiota and insulin signalling pathways. Serum metabolite signatures, specifically increased abundance of branched-chain amino acids (BCAAs), which are unable to be synthesized by humans and therefore must be obtained from the diet or derived from microbial metabolism, have been associated with insulin resistance in two independent studies [120, 121]. In a series of follow-up experiments utilizing a high-fat fed murine model, the authors of one study demonstrated that challenging mice with *Prevotella copri*, a species identified as synthesizing BCAAs, over three weeks resulted in increased circulating BCAA concentrations and exacerbated insulin resistance [121]. Another metabolite, imidazole propionate, which is a byproduct of the microbial metabolism of dietary histidine, was also found at higher circulating concentrations in individuals with type 2 diabetes and was associated with severity of insulin resistance [122]. Interestingly, in a murine model, administration of imidazole propionate impaired glucose tolerance independent of changes in insulin concentrations; subsequent *in vitro* experiments revealed alterations in phosphorylation of the insulin receptor substrate (IRS) and activation of the mechanistic target of rapamycin complex (mTORC1) in response to imidazole propionate [123]. These insights provide early evidence of a causal link between the gut microbiota and alterations in insulin signalling pathways.

The microbiome contributes to type 2 diabetes risk via innate immune pathways

As a key component of Gram-negative pathogenic strains, LPS is recognized by pattern recognition receptors that play a critical role in the activation of immune and inflammatory pathways. Immune responses to circulating LPS are well characterized in models of infection and sepsis, but activation of similar signalling pathways would also be anticipated in metabolic endotoxaemia and understanding these pathways provides insights into how the intestinal microbiota contribute to risk for type 2 diabetes. Regardless of the trigger for LPS translocation, once in the circulation LPS binds to LPS-binding protein (LPB), a constitutively expressed plasma protein, which facilitates the interaction between LPS and various receptors and binding sites. Among these receptors are the toll-like receptor 4 (TLR4) cell surface molecule and its associated co-receptor, cluster of differentiation 14 (CD14). TLR4 activation initiates an extensive intracellular signalling cascade that initially involves recruitment of the MyD88 adaptor protein and activation of IL-1R1-associated protein kinases (IRAKs) [124], which can trigger (i) subsequent phosphorylation of IKB kinase (IKK-B), the degradation of IKB and NF-KB translocation to the nucleus to facilitate transcriptional regulation of inflammatory mediators, including interleukin (IL)-1, tumour necrosis factor (TNF)-α, and IL-6 [125]; and (ii) c-Jun NH2-terminal kinase (JNK) activation [126]. Interestingly, saturated fatty acids also act as ligands for TLR4 [124] and provide an additional stimulus for initiating these same signalling pathways in obesity.

The crosstalk between TLR4 and insulin signalling pathways provide a mechanism linking the intestinal microbiota to insulin resistance (Figure 19.2). Classic insulin signalling pathways involve a complex series of phosphorylation events initiated by the interaction between insulin and its cell surface receptor. Receptor-ligand binding triggers the autophosphorylation of the intracellular domain of the insulin receptor and subsequent phosphorylation (predominantly at tyrosine residues) of the intracellular IRS family members with additional kinase activity, including Akt involvement, culminating in the exocytosis of glucose transporters to the cell surface to facilitate glucose uptake [127]. Insulin signalling can be regulated by a negative feedback loop where phosphorylation of IRS members (predominantly at serine/threonine residues) inhibits further signal transduction, essentially impeding further cellular glucose uptake [128, 129]. Insulin signalling pathways also contribute to the regulation of glycogen synthesis (via glycogen synthase activation [127]) and regulation of metabolic pathways (via transcription factor regulation [128]) and in this way contribute to glucose homeostasis more globally beyond cellular glucose uptake.

Signalling cascades initiated by LPS-TLR4 binding have the potential to regulate the insulin signalling pathways at multiple points. Notably, JNK activation downstream of TLR4 activation can trigger phosphorylation of IRS members at serine/threonine residues, inhibiting further insulin signalling [130, 131]. Additional triggers have been identified for JNK activation and subsequent disruption of insulin signalling, notably endoplasmic reticulum (ER) stress [132, 133]; while these pathways are also relevant in understanding the pathogenesis of type 2 diabetes, particularly in the context of obesity and nutrient excess, these is little evidence suggesting direct modulation by the intestinal microbiota. However, inflammatory cytokines secreted in response to TLR4 signalling and as part of the unfolded protein response can signal back to cells in an autocrine or paracrine fashion and, via their own cell surface receptors, trigger further activation of the JNK pathway, contributing to a cycle of persistent amelioration of insulin signalling [134, 135].

Indeed, studies involving animal knockout models, loss-of-function mutations, and receptor antagonists provide support for the involvement of the TLR4 and JNK pathways in linking the microbiome and insulin resistance. Animal models involving TLR4 mutants or knockouts [136, 137] and a human clinical trial involving infusion of an anti-CD14 antibody [138, 139] all demonstrate attenuated inflammatory responses to LPS exposure, confirming the role of TLR4/CD14 signalling in mediating the inflammatory response to LPS exposure. Similarly, the murine model mentioned earlier whereby LPS infusion was sufficient to trigger changes in insulin sensitivity and glucose

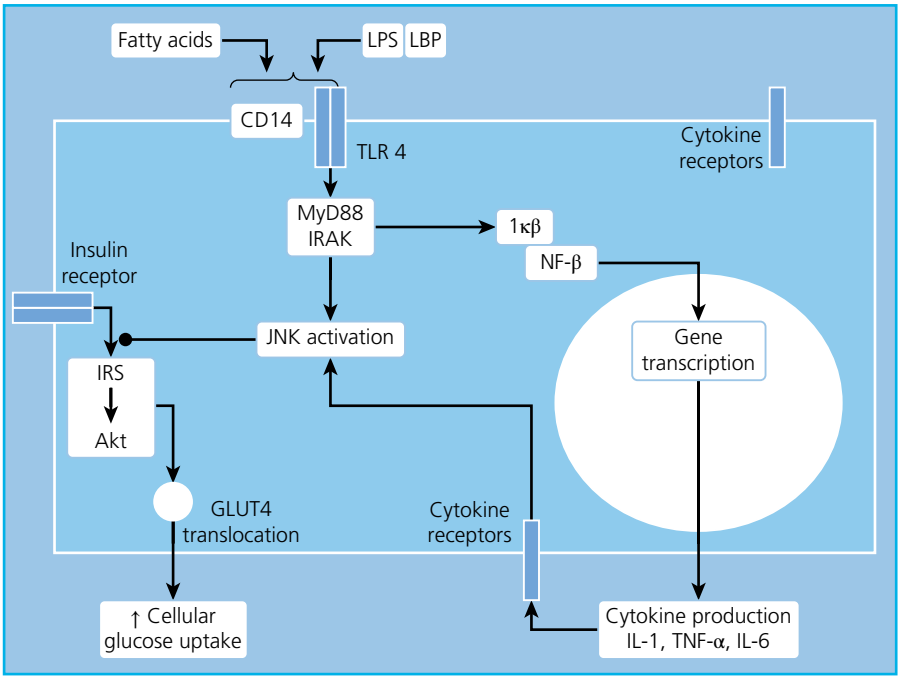

Figure 19.2 Components of the intestinal microbiota (namely lipopolysaccharide, LPS) have the potential to activate innate immune pathways. Crosstalk between toll-like receptor 4 (TLR4) and insulin signalling pathways provides a mechanism linking the intestinal microbiota to insulin resistance. CD14, cluster of differentiation 14; GLUT4, glucose transporter 4; IL, interleukin; IRAK, IL-1R1-associated protein kinases; IRS, insulin receptor substrate; JNK, c-Jun NH2-terminal kinase; LBP, lipopolysaccharide-binding protein; LPS, lipopolysaccharide; TNF, tumour necrosis factor.

levels also demonstrated that this series of responses was attenuated in CD14-deficient mice [72]. These findings are consistent with those from a murine model with a TLR4 loss-of-function mutation and utilizing a high-fat feeding protocol; the downregulated TLR4/CD14 signalling pathway was protective for metabolic dysregulation and was associated with attenuated IKKB and JNK signalling [140]. Similarly, JNK knockout mice are protected from insulin resistance triggered by high-fat feeding [141] and in an obese diabetic mouse model administered a JNK inhibitory peptide, lower fasting glucose and insulin concentrations and improved insulin sensitivity in response to glucose and insulin tolerance tests have been reported [142]. While these findings are from animal studies only, collectively these data highlight key signalling pathways that link the intestinal microbiome and risk for type 2 diabetes.

The microbiome contributes to type 2 diabetes risk via modulation of enteroendocrine cell function

Beyond the purported roles of bacterial fermentation products in promoting colonocyte health [143], identification of the signalling pathways via which SCFAs may contribute to metabolic regulation further implicate the intestinal microbiome in the pathogenesis of type 2 diabetes. SCFAs have been identified as ligands for a series of G-protein–coupled receptors (GPRs) expressed on the intestinal epithelium as well as by adipose tissue and immune cells [144]. SCFAs differentially activate various GPRs: propionate shows the highest affinity for GPR41 (also known as free fatty acid receptor 3) and GRP43 (also known as free fatty acid receptor 2), acetate for GPR43, and butyrate for GPR41 and GPR109A [145]. Activated downstream signalling pathways include those implicated in enteroendocrine cell function [146, 147], as discussed shortly (Figure 19.3), as well the regulation of immunity and inflammation [148], which has the potential to influence insulin signalling pathways.

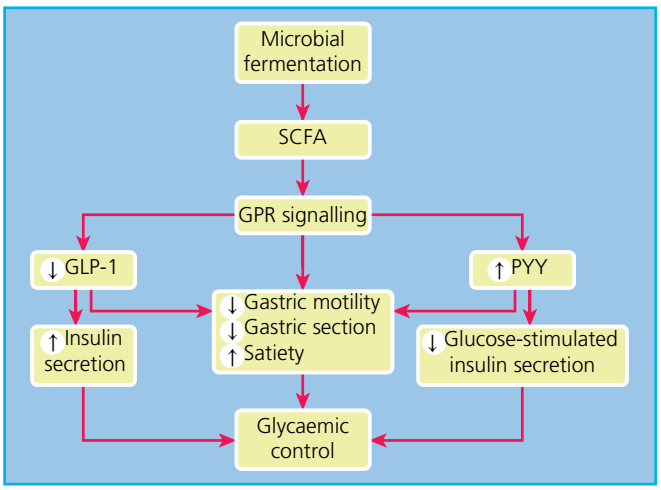

Figure 19.3 Short-chain fatty acids (SCFA) are produced during microbial fermentation of non-digestible dietary starches. SCFA signalling via G-protein–coupled receptors (GPR) can regulate incretin signalling, namely glucagon-like peptide 1 (GLP-1) and polypeptide YY (PYY), with downstream effects on glycaemic levels.

Potential regulation of enteroendocrine function, particularly glucagon-like peptide-1 (GLP-1) and polypeptide YY (PYY) secretion, may be especially relevant when considering the role of the intestinal microbiome in type 2 diabetes pathogenesis. GLP-1 and PYY are co-secreted from enteroendocrine cells resident in the colonic mucosa in response to nutrient sensing [149, 150]. Some effects of GLP-1 and PYY are similar, including attenuation of gastrointestinal motility and gastric acid secretion [149, 151] and induction of satiety, likely via centrally mediated mechanisms [152, 153]. However, GLP-1 and PYY have opposing effects on insulin secretion. GLP-1 acts to increase glucose-stimulated insulin secretion [151, 152], whereas PYY has been shown to inhibit glucose-stimulated insulin release from the pancreas [154]. Both GLP-1 and PPY undergo enzymatic cleavage by dipeptidyl peptidase (DPP)-4; for

GLP-1 this plays a role in clearance of the active form [155], but for PYY this generates the biologically active form [154]. Given the documented effects of GLP-1 and PPY in the context of glucose metabolism, it is not surprising that both GLP agonists and DPP-4 inhibitors have been developed for the treatment of type 2 diabetes [156].

The potential for the intestinal microbiome, via SCFA, to modulate GLP-1 and PPY secretion [157] represents a further pathway via which the intestinal microbiome may contribute to risk insulin resistance and type 2 diabetes. *In vitro* and animal models and human supplementation studies support this possibility. In primary colonic cultures from wild-type mice, treatment with SCFA induced GLP-1 secretion, an effect that was attenuated in tissue from GPR41 and GPR43 knockout mice [147]. Similarly, more pronounced impairments in plasma GLP-1 in response to oral glucose load were noted in the knockout animals [147], further supporting SCFA-induced signalling via GPR41/43 as a key trigger for incretin secretion. Additional studies in rodent models assessing both GLP-1 and PYY responses to SCFA reported similar outcomes for both primary colonic cultures [158] and isolated perfused colon preparations [159]. Interestingly, use of prebiotic fermentable fibre supplements, to increase colonic production of SCFAs, have not resulted in increased GLP-1 or PYY secretion in acute single-meal interventions [160, 161]. However, several small-scale studies in otherwise healthy adults have reported higher glucose-induced plasma concentrations of PYY [162] and GLP-1 [163, 164] following 2–12 weeks of prebiotic supplementation. Similarly, a 6-week prebiotic supplementation study in adults with overweight or obese also found increased post-prandial GLP-1 and PYY secretion at the end of the intervention period [165], while a longer 12-month supplementation study involving hyperinsulinaemic adults (n = 40) and supplementation with dietary high-fibre cereal (a form of non-digestible starch and a substrate for the intestinal microbiota) reported significant increases in plasma SCFAs and increases in both basal and post-prandial GLP-1 concentrations [166]. These data generally support an association between SCFA and GLP-1 and PYY, and highlight the need for further consideration of the value of modulation of the intestinal microbiota to mitigate disrupted incretin signalling in metabolic disease.

The microbiome contributes to type 2 diabetes risk via modulation of bile acids

The role of bile acids in lipid digestion and absorption is well established, with bile acid turnover providing a pathway for cholesterol excretion [167]. Beyond these actions, regulatory roles of bile acids in glucose metabolism have also been acknowledged. Bile acid composition has been associated with features of insulin resistance in European adults [168] and altered bile acid composition has also been noted in adults with diabetes [169, 170]. Further, over recent years, clinical trials have demonstrated the effects of bile acid sequestrants on glucose metabolism. A pair of meta-analyses have both reported positive effects of bile acid sequestrants on measures of glucose metabolism, including fasting blood glucose and HbA_{1c} [171, 172], which broadly supports an association between regulation of the bile acid pool and glucose control.

While the exact mechanisms linking the bile acid pool and glucose metabolism are yet to be fully defined, two pathways have received particular attention (Figure 19.4). Bile acids are known ligands for the nuclear receptor farnesoid X receptor (FXR), which activates the transcription factor short heterodimer protein (SHP) [173] and regulates the expression of a number of genes involved in bile acid synthesis and metabolism, thereby establishing a feedback loop facilitating bile acid self-regulation [167, 174, 175]. FXR-mediated signalling has been associated with glucose homeostasis [167]. FXR receptor knockout mice have impaired plasma glucose clearance in response to both glucose and insulin tolerance tests [176, 177]. Conversely, administration of FXR agonists in a diabetic mouse model decreases fasting glucose and insulin [178], suggesting preserved insulin sensitivity. In both settings, intracellular signalling pathways were also examined and either decreased (in the FXR knockouts) or increased (in response to FXR agonist) Akt phosphorylation was reported [176, 178], suggesting that FXR signalling may contribute directly to regulation of insulin signalling pathways. Other studies have implicated FXR in the downregulation of genes involved in hepatic gluconeogenesis [177, 179], as well in glucose-induced insulin secretion from pancreatic β cells

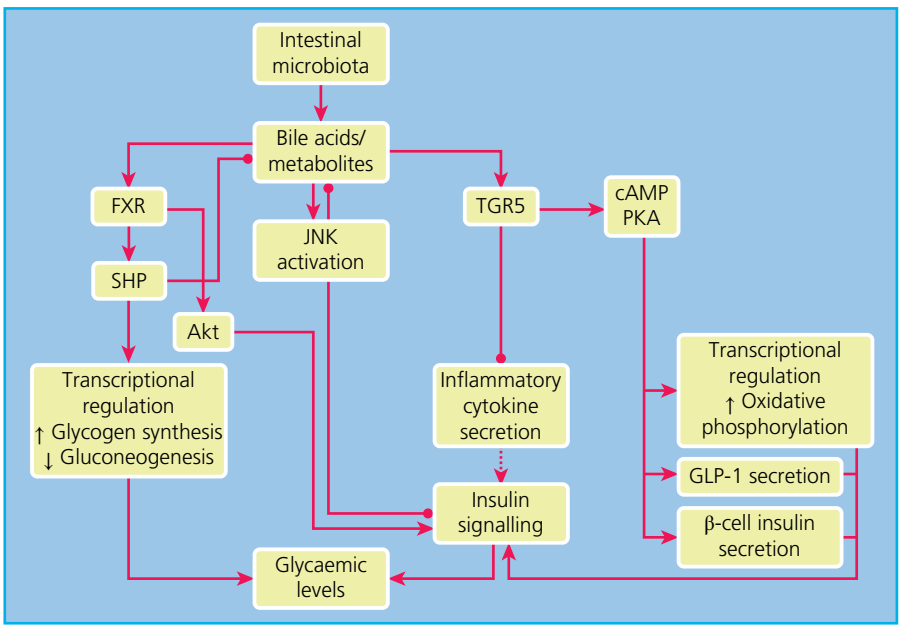

Figure 19.4 The intestinal microbiome influences composition of the bile acid pool and metabolites. Bile acid signalling through the farnesoid X receptor (FXR) and the G-protein–coupled receptor (TGR5) pathways can affect transcriptional regulation of various metabolic pathways. Regulation of other signalling pathways can also contribute to alterations in glycaemic control. cAMP, cyclic adenosine monophosphate; GLP-1, glucagon-like peptide 1; JNK, c-Jun NH2-terminal kinase; PKA, protein kinase; SHP, short heterodimer protein.

[180, 181], providing further mechanisms via which bile acids may contribute to insulin resistance.

In addition to signalling via FXR, bile acids have also been identified as a ligand for the G-protein–coupled bile acid receptor (TGR5) [182, 183]. Activated intracellular signalling pathways are thought to involve protein kinase A and the cyclic AMP response element binding protein, which can regulate gene expression and allows for a range of downstream effects [174]. In the context of insulin resistance, *in vitro* models have shown that bile acid signalling can induce GLP-1 secretion from enteroendocrine and primary intestinal cell cultures, with small interfering RNAs and TGR5 agonists confirming that these responses are mediated via TGR5 activation [184, 185]. Animal models also support a role for TGR5 signalling in mediating glucose homeostasis [186]. Use of selective TGR5 agonists in high-fat fed mice decreases plasma glucose and insulin and improves glucose clearance rates in glucose tolerance tests [187, 188]. Further, TGR5 overexpression in a transgenic mouse model resulted in improved glucose clearance rates in a glucose tolerance test and augmented post-prandial GLP-1 and insulin secretion, whereas glucose tolerance and GLP-1 secretion were impaired in TGR5 knockout animals [188]. In some human clinical studies involving bile acid sequestrants, GLP-1 responses have been shown to parallel changes in insulin sensitivity [189], further supporting GLP-1 as a link between bile acid signalling and risk for diabetes. Finally, evidence suggesting that TGR5 activation by bile acids may have inhibitory effects on inflammatory cytokine production [183, 190] provides a further mechanism via which bile acid signalling may indirectly contribute to the regulation of insulin signalling pathways.

Given the potential for bile acids to contribute to glucose regulation, modulation of the bile acid pool by the intestinal microbiota provides another interface between the microbiota and risk for diabetes. While enterohepatic circulation recovers a large proportion of secreted bile acids from the distal ileum, a proportion reach the large bowel where the microbiota catalyse a series of reactions, including deconjugation, dehydrogenation, and dehydroxylation reactions, resulting in the formation of secondary bile acids [191, 192]. Secondary bile acids may themselves contribute to the feedback inhibition of bile acid synthesis and secretion, and other downstream effects via the FXR and TGR5 signalling pathways [193, 194]. Animal models support the involvement of the intestinal microbiota in modulation of the bile acid pool, with the composition of the bile acid pool shown to differ between germ-free and conventionalized animals in both rodent [195] and murine models [196]. Further, in several rodent and murine models, antibiotic treatment modulates the composition of the bile acid pool in favour of primary bile acids [197, 198] and upregulates FXR signalling pathways [199, 200]. Modulation of the intestinal microbiota in humans also influences composition of the bile acid pool. Of particular interest is a seven-day antibiotic intervention in 20 men with obesity, whereby a reduction in faecal secondary bile acids was noted and alterations in bile acid composition were correlated with alterations in peripheral insulin sensitivity pre- to post-intervention [201]. These findings have been broadly replicated in a larger cohort (n = 57) of men with overweight or obese [202]. Gut microbial manipulation via probiotic and prebiotic intervention also alters bile acid metabolism. In one study involving 134 adults with overweight or obese in a parallel (four) group design, a reduction in plasma concentrations of specific primary and secondary conjugated bile acids were reported following six months of supplementation with a synbiotic supplement [203]. Similarly, a placebo-controlled crossover trial of three probiotic supplements over six-week intervention periods in adults with obesity (n = 103) resulted in increases in total plasma deconjugated bile acids in response to *Bacillus subtilis* and *Bifidobacterium animalis* subspecies *lactis* supplements [204]. Although the bile acid signalling pathways are complex, effects on glucose levels are plausible and, given the established roles of the intestinal microbiota in regulating the composition of the bile acid pool, contributions of the intestinal microbiota to risk for type 2 diabetes via these pathways cannot be discounted.

Type 1 diabetes

It would be remiss to ignore a potential role of the intestinal microbiota in the pathogenesis of type 1 diabetes. While the precise mechanisms and molecular signalling pathways remain under investigation, support for the interplay between the intestinal microbiota, intestinal permeability, and immune aberrations in initiating the autoimmune destruction of pancreatic β cells continues to grow [205, 206]. Reduced microbial diversity and differences in the composition of the intestinal microbiota between individuals with and without type 1 diabetes are documented [207], suggesting, at minimum, an association between the intestinal microbiota and type 1 diabetes risk. Studies involving germ-free animal models that report increased type 1 diabetes incidence [208] support the importance of a robust intestinal microbiome in mitigating type 1 diabetes risk. Similarly, animal models demonstrating that modulation of the intestinal microbiota, using either antibiotics [209] or probiotic supplementation [210], results in delayed onset and reduced incidence of diabetes provide further evidence in support of a potential link between gut microbiome and type 1 diabetes risk. Alterations in intestinal permeability have also been noted in both animal models of type 1 diabetes [211, 212] and human clinical studies [213, 214], and provide insight into the mechanisms that may link the intestinal microbiome and type 1 diabetes. Given the identified roles of butyrate-producing bacterial strains in promoting the integrity of the intestinal mucosa [66, 67], alterations in microbial composition may underpin diminished mucosal integrity in type 1 diabetes. Increased intestinal permeability and associated translocation of LPS and other antigens across the mucosal surface may trigger aberrations in immune regulation and the development of autoimmune responses in genetically susceptible individuals.

The role of the microbiota in shaping host immune development can also not be overlooked in the context of type 1 diabetes risk. The increased prevalence of type 1 diabetes in developed nations has been interpreted by some to support the hygiene hypothesis, whereby inappropriate immune development in response to limited microbial exposure is considered a risk factor for the development of autoimmunity [215]. Immunological aberrations reported previously in type 1 diabetes include reduction in FoxP3+ regulatory T cells (Tregs) in the intestinal mucosa [216], reduction in peripheral T regs [217] and natural killer (NK) T cells [217], and dysregulated cytokine signalling, suggestive of impaired T-cell function [218] in individuals with type 1 diabetes. T helper 17 (Th17) responses have also received particular attention for their roles in inflammatory control and autoimmune disease [219, 220], and an upregulation of peripheral Th17 cells has been reported in individuals with type 1 diabetes [221]. Of further interest is the growing recognition of the role of the intestinal microbiota in regulating Th17 and Treg phenotypes [222, 223]; although the precise mechanisms underpinning these effects are yet to be elucidated,

these associations do further implicate the intestinal microbiome, via modulation of the immune system, in risk for type 1 diabetes.

Conclusion and perspectives

Given the considerable size of the metagenome and associated metabolic machinery, it is not surprising that the interface between intestinal microbiome and human host has the potential to have impacts on health, including risk for disease. The potential for crosstalk between the microbiome and immunological and metabolic pathways is relevant in type 2 diabetes; activation of innate immune pathways, modulation of enteroendocrine cell function, and regulation of metabolic signalling pathways by the microbiome all have the potential to disrupt insulin signalling pathways and contribute to impaired glucose metabolism. In the context of type 1 diabetes, inappropriate immune education by the microbiome may potentiate autoimmune destruction of pancreatic β cells in otherwise susceptible individuals, thereby increasing risk. Given the increasing prevalence of both type 1 diabetes and type 2 diabetes, particularly in the developed world, understanding the molecular mechanisms by which the microbiome contributes to risk for diabetes may prove beneficial in the development of additional risk-stratification tools. Further, the potential to manipulate the composition of the microbiome may enhance existing treatment and management strategies.

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4 Other Types of Diabetes

20 Monogenic Causes of Diabetes

Brittany L. Resnick[1], Maggie H. Shepherd[1,2], and Andrew T. Hattersley[2]

[1] Exeter NIHR Clinical Research Facility, Royal Devon University Healthcare NHS Foundation Trust, Exeter, UK

[2] Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter, UK

Key points

- Monogenic diabetes should be suspected where:
  - presentation is atypical for type 1 diabetes or type 2 diabetes;
  - there is an autosomal dominant family history or maternally inherited diabetes in mitochondrial disorders;
  - there are characteristic associated features such as deafness in mitochondrial diabetes or fat loss in lipodystrophy; or
  - diabetes has been diagnosed within the first six months of life.
- Variants in the glucokinase gene, which is important in sensing blood glucose levels in the pancreas, result in resetting of fasting glucose to a higher level (5.5–8.0 mmol/l; 90–145 mg/dl). People with glucokinase variants have dominantly inherited mild fasting hyperglycaemia with only modest changes in glycated haemoglobin. Complications are rare and no treatment is needed.
- Variants in the transcription factor genes *HNF1A* and *HNF4A* result in dominantly inherited progressive hyperglycaemia with symptomatic diabetes in adolescence or young adulthood. People with *HNF1A* or *HNF4A* diabetes are very sensitive to sulfonylurea treatment and may not require insulin until middle or old age.
- Mitochondrial variants can result in maternally inherited diabetes, often with bilateral sensorineural hearing loss and a range of other disorders.
- Diabetes diagnosed before 6 months of age is very unlikely to be type 1 diabetes and a genetic cause should be sought even where the person is now an adult. High-dose sulfonylurea treatment is often more effective than insulin where variants affecting Kir6.2 and SUR1 subunits of the β-cell potassium channel are identified.
- Acanthosis nigricans is the key feature of insulin resistance and a genetic cause should be considered where there is no concomitant obesity. Partial lipodystrophy results in thin muscular limbs with hypertriglyceridemia and insulin resistance and suggests a variant in *LMNA* or *PPARG*. In the absence of lipodystrophy, an insulin receptor variant is the commonest cause.

Monogenic diabetes results from inheritance of one or more variants in a single gene and accounts for 1–3% of diabetes cases diagnosed under the age of 30 years. Variants may be inherited in a dominant or recessive fashion. The majority (90%) of monogenic diabetes cases are initially misdiagnosed as type 1 diabetes or type 2 diabetes. Correct genetic diagnosis is important to predict clinical course, explain other associated clinical features, enable genetic counselling, diagnose family members, and most importantly guide appropriate treatment.

Monogenic diabetes where the primary disorder affects the β cell has four main clinical presentations:

- Familial mild fasting hyperglycaemia (glucokinase maturity-onset diabetes of the young, MODY).
- Familial young-onset diabetes (transcription factor MODY).
- Neonatal diabetes.
- Diabetes with extra-pancreatic features.

Clinical and biochemical features that help differentiate the common forms of monogenic diabetes that result in β-cell dysfunction from type 1 diabetes and type 2 diabetes are summarized in Table 20.1. Classification and key features of monogenic diabetes are further summarized in Figure 20.1 and their role in β-cell physiology is depicted in Figure 20.2. Single-gene variants may also cause diabetes through insulin resistance, as occurs in the inherited lipodystrophies and insulin receptor variants. A number of monogenic multisystem diseases (e.g. haemochromatosis and cystic fibrosis) may cause diabetes; these are beyond the scope of this chapter and are discussed elsewhere (Chapter 23).

Maturity-onset diabetes of the young

MODY is autosomal dominantly inherited diabetes that, despite a young age of onset, is not insulin dependent [2, 3]. It results from β-cell dysfunction rather than insulin resistance [2]. The underlying genetic aetiology has now been defined, allowing MODY to be subclassified according to the gene involved [4, 5]. Variants in at least 11 genes have been linked to MODY [1, 6, 7]. These include variants in the gene encoding the glucose-sensing enzyme glucokinase (*GCK*) and variants in several transcription factors that affect β-cell development and function, the frequencies of which are summarized in Figure 20.3. Clinical presentation varies greatly depending on the underlying genetic variant. Table 20.2 summarizes the clinical features of glucokinase and transcription factor diabetes. The strikingly different subtypes of MODY mean it is important to define the underlying genetic aetiology. We recommend the use of clinical categories based on underlying genetic cause, for example familial mild fasting

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Table 20.1 Differentiating β-cell monogenic diabetes from type 1 diabetes and 2 diabetes.

Features	Type 1 diabetes	Young type 2 diabetes	*GCK* MODY	*HNF1A* MODY	MIDD	K_{ATP} PNDM
Optimal treatment	Insulin	OAD	None	Low-dose SU	Insulin	High-dose SU
Parent affected	2–4%	Usually (may have both parents affected)	Yes	Yes	Mother	15%
Typical age of onset	6 mo to adult	Adolescent and young adult	Birth (may be diagnosed at any age)	Adolescent to young adult	Young adult	Under 6 mo
Obesity	Pop freq	Yes	Pop freq	Pop freq	Rare	Pop freq
Acanthosis nigricans	No	Yes	No	No	No	No
Glycaemia	High	Variable	Mild	High	Variable	High
β-cell autoantibodies	Yes (90% of cases)	No	No	No	No	No

GCK, glucokinase; *HNF1A*, hepatocyte nuclear factor 1A (*HNF4A* is similar); MIDD, maternally inherited diabetes and deafness; MODY, maturity-onset diabetes of the young; OAD, oral anti-diabetes drugs; PNDM, permanent neonatal diabetes; Pop freq, population frequency (frequency of obesity seen in the general population); SU, sulfonylureas.

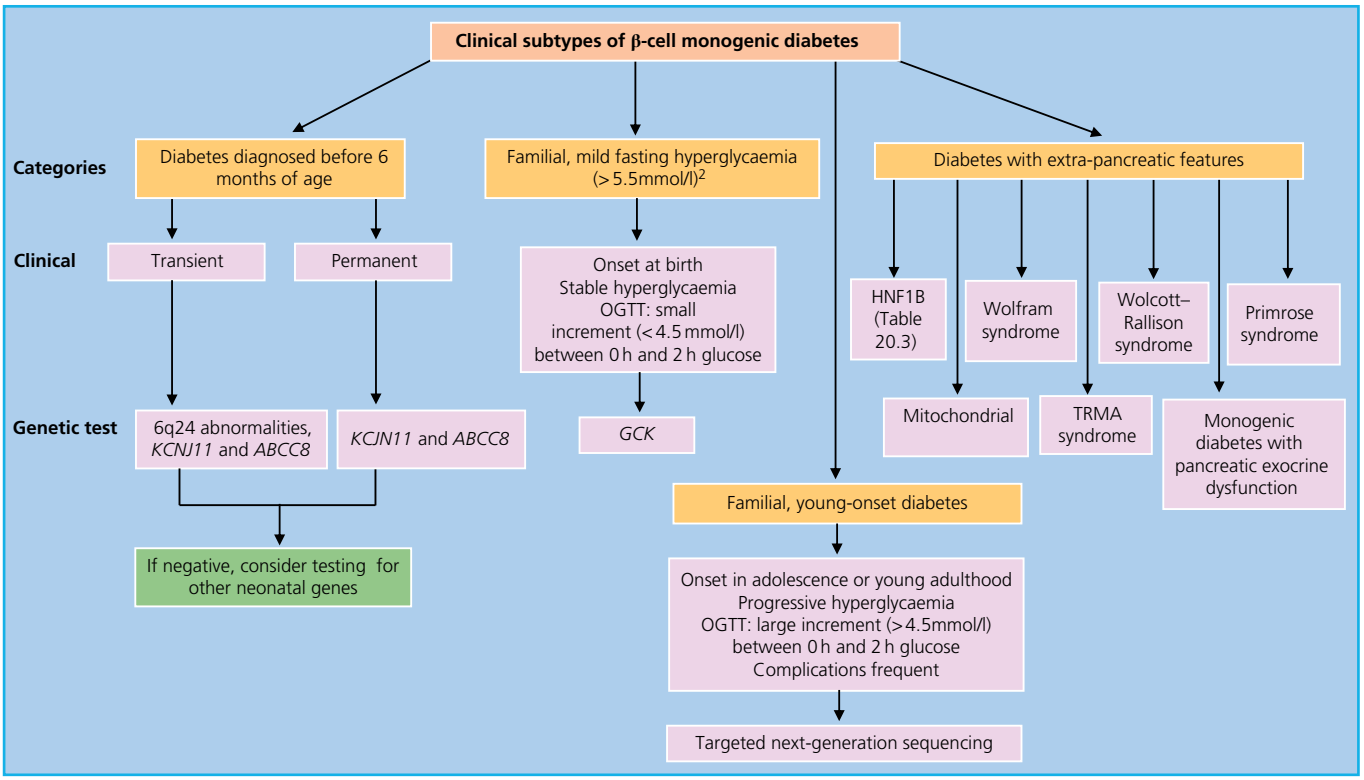

Figure 20.1 Clinical subtypes of monogenic β-cell diabetes. To convert plasma glucose measurements to mg/dl, multiply by 18. *ABCC8*, ATP binding cassette subfamily C; *GCK*, glucokinase gene; HNF, hepatocyte nuclear factor; *KCNJ11*, potassium inwardly rectifying channel, subfamily J, member 11 gene; OGTT, oral glucose tolerance test; TRMA, thiamine responsive megaloblastic anaemia.

hyperglycaemia resulting from glucokinase gene variants (*GCK* MODY), familial young-onset progressive diabetes resulting from *HNF1A* and *HNF4A* variants (transcription factor MODY), and renal cysts and diabetes syndrome (RCAD) resulting from *HNF1B* variants.

Variants in the genes associated with MODY should be considered in people with diabetes diagnosed under 25 years of age who do not fully fit the phenotypes of type 1 diabetes or type 2 diabetes and who have a strong family history of diabetes (Table 20.1). Differentiating from apparent type 1 diabetes is particularly important, as these individuals can often be most effectively treated without the use of injected insulin. The differentiation of MODY from other types of diabetes is challenging and attention has turned to strategies that will enable better stratification of those requiring genetic testing, which include the use of a probability calculator (available at www.diabetesgenes.org to view and to download as a phone application), measurement of C-peptide and autoantibodies, as well as advances in genetic testing that allow panels of genes to be tested simultaneously using targeted next-generation sequencing.

Prevalence of MODY variants

MODY was previously indicated to have a minimum population prevalence of 108 cases per million, but this was recognized as an underestimate [8]. Prevalence estimates from large systematic surveys are between 1% and 3% of young-onset diabetes; in the UK Using

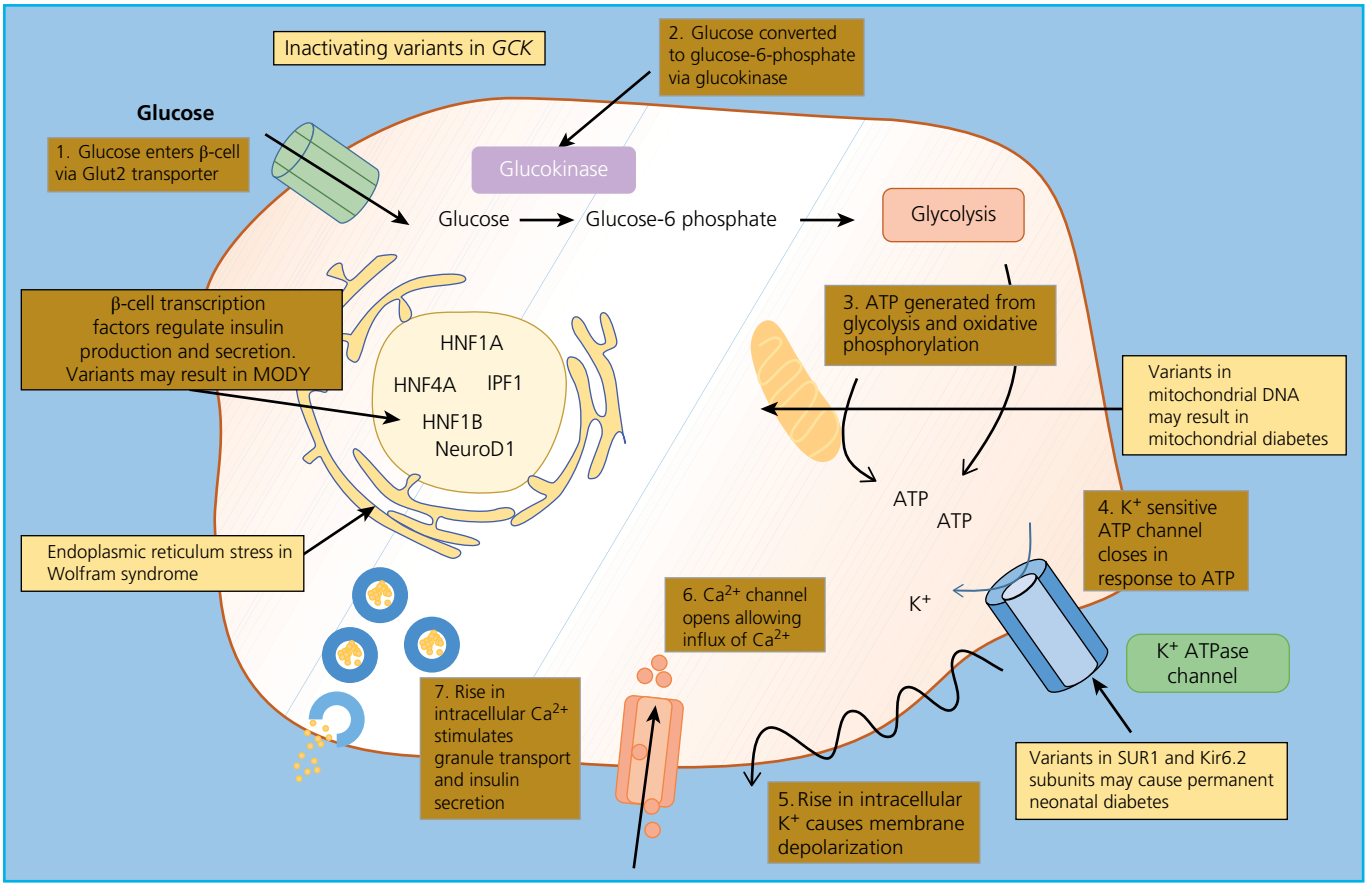

Figure 20.2 Schematic of β-cell depicting key steps in glucose sensing and insulin secretion (brown boxes) and transcription factors, enzymes, organelles, and protein channels that may, if mutated, be a cause of monogenic diabetes (pale yellow boxes). ATP, adenosine triphosphate; *GCK*, glucokinase gene; MODY, maturity-onset diabetes of the young. Source: Adapted from Fajans et al. [1].

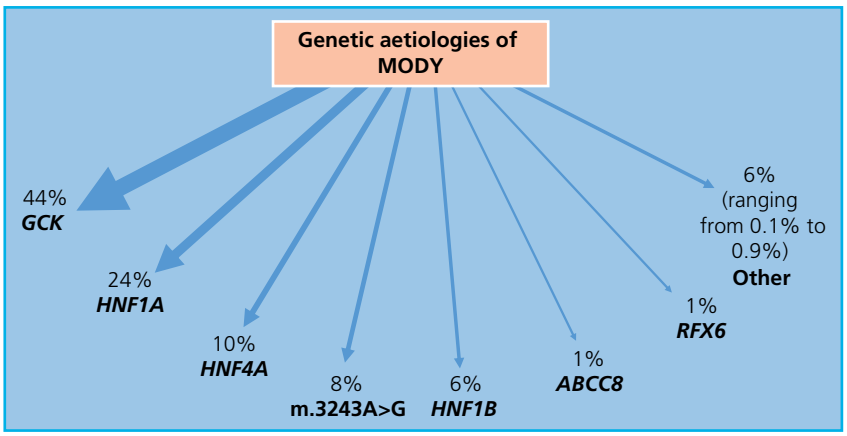

Figure 20.3 The different genetic aetiologies in a UK maturity-onset diabetes of the young (MODY) series from the Exeter Molecular Genomics Laboratory at the Royal Devon and Exeter NHS Foundation Trust, UK, from 2015 to 2020. Other includes *WFS1*, *INSR*, *PPARG*, *INS*, *LMNA*, *PDX1*, *KCNJ11*, *NEUROD1*, *GATA6*, *SLC19A2*, and *TRMT10A* subtypes. Source: Personal communication from Kevin Colclough.

pharmacogeNetics to Improve Treatment in Early-onset Diabetes (UNITED) study, 3.6% of all diabetes diagnosed <30 years of age [9] and 2.5% of all diabetes diagnosed <20 years of age were MODY [10], while the SEARCH for Diabetes in Youth study undertaken in the USA found that 1.2% of all cases diagnosed under 20 years of age were MODY [11]. A population study based on screening pregnant women estimated the glucokinase prevalence to be 1.1 in 1000 population prevalence (or 1100 cases/million population) [12], suggesting that most people with glucokinase variants are not coming to medical attention or are not being diagnosed. Based on previous estimates of MODY prevalence, 80–90% of cases were likely to be misdiagnosed or unrecognized, highlighting the need for improved case finding.

Strategies to improve case finding

The key approach to diagnosing MODY is to consider whether there are clinical features that are unusual for type 1 diabetes and type 2 diabetes and to undertake genetic testing in these individuals to confirm monogenic diabetes (Figure 20.4). Though the cost of

Table 20.2 Comparison of the clinical characteristics of glucokinase and transcription factor maturity-onset diabetes of the young (MODY).

	Glucokinase MODY	Transcription factor MODY
Onset of hyperglycaemia	Birth	Adolescence/early adulthood
Presentation	Usually asymptomatic, detected by screening or on routine testing	Usually symptomatic
Nature of hyperglycaemia	Minimal increase in glycaemia with age Mild (FPG usually 5.4–8.3 mmol/l) HbA_{1c} 40–60 mmol/mol (5.8–7.6%)	Progressive deterioration of glycaemia with age May be severe (FPG frequently >14 mmol/l off treatment) HbA_{1c} variable depending on age and treatment, may be high
Pattern in an oral glucose tolerance test	FPG >5.5 mmol/l (2 h FPG) 2 h increment usually <3.5 mmol/l	FPG often <5.5 mmol/l (2 h FPG) 2 h increment usually >3.5 mmol/l
Microvascular complications	Rare	Frequent
Pathophysiology	β-cell defect (glucose sensing defect)	β-cell defect (initially insulin secretion maintained at normal glucose values but not increased in hyperglycaemia)
Extra-pancreatic manifestations	Altered birth weight	See Table 20.3
Treatment	Pharmacological treatment rarely needed	Sensitive to sulfonylurea treatment May progress to require insulin

FPG, fasting plasma glucose – to convert plasma glucose measurements to mg/dl multiply by 18; HbA_{1c}, glycated haemoglobin.

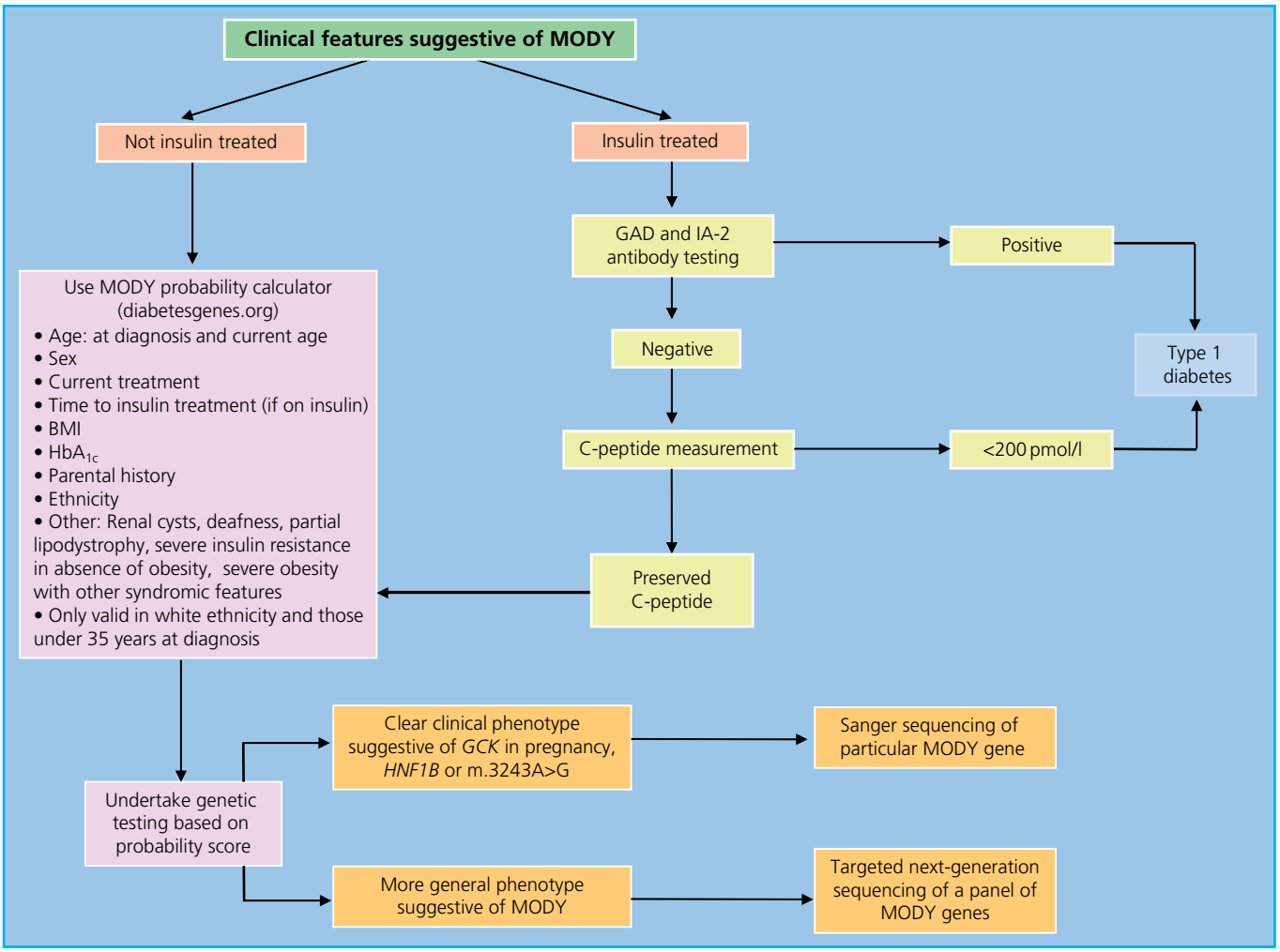

Figure 20.4 An approach to genetic testing in people with suspected MODY mutations. BMI, body mass index; GAD, glutamic acid decarboxylase; HbA_{1C}, glycated haemoglobin; IA-2, islet antigen 2. Source: Shields et al. [13] and De Franco et al. [14].

molecular testing continues to fall, it is still relatively expensive and it is therefore recommended that testing is restricted to those individuals with a moderate to high possibility of a positive result. Traditional clinical features, such as age at onset, a parental history of diabetes, and non-insulin treatment, overlap considerably between MODY and other types of diabetes [8] and therefore independently have poor discriminatory value.

A MODY probability calculator (available at www.diabetesgenes.org) offers an excellent way to establish if a diagnosis of MODY is likely: it combines clinical information to predict the probability of testing positive for MODY [13]. The calculator markedly improved the sensitivity and specificity of identifying MODY compared with standard criteria of diagnosis age <25 years with an affected parent.

Biomarkers such as C-peptide measurement, pancreatic autoantibodies, lipid profiles, and high-sensitive C-reactive protein (CRP) all have some discriminatory value in differentiating cases of MODY from other subtypes; however, they are not without limitations [15–20]. Pancreatic autoantibodies are positive close to diagnosis in approximately 90% of people with type 1 diabetes if glutamic acid decarboxylase (GAD), islet antigen 2 (IA2), and zinc transporter 8 (ZnT8) antibodies are measured, compared to only 1% of those with MODY [17]. A negative test does not exclude type 1 diabetes, especially as with increasing duration of diabetes antibody positivity is lost. Testing pancreatic autoantibodies in people treated with insulin is therefore of value, if positive, in excluding MODY. The presence of preserved C-peptide secretion in a person with type 1 diabetes of long duration may also help stratify those in whom MODY testing should be considered; however, 8% of people with long-term type 1 diabetes have stimulated C-peptide levels of >200 pmol/l [21]. Utilization of non-invasive urinary C-peptide to creatinine ratios assists in differentiating MODY from type 1 diabetes and avoids the need for blood samples [16]. In the paediatric population, the Swedish Better Diabetes Diagnosis (BDD) study found that absence of all pancreatic autoantibodies and modest hyperglycaemia (glycated haemoglobin [HbA_{1c}] 58 mmol/mol; <7.5%) at diagnosis of diabetes were discriminatory clinical features of MODY from type 1 diabetes and should lead to genetic testing [22]. This again emphasizes that antibody testing is helpful since a positive result excludes MODY.

New discriminatory tools have been developed to aid differentiation of MODY from type 1 diabetes, including the type 1 diabetes genetic risk score [23]. The type 1 diabetes genetic risk score is generated by genotyping common genetic variants associated with an increased risk of type 1 diabetes and summing their effective weight into a numerical score [23, 24].

Use of diagnostic and pre-symptomatic molecular testing in monogenic diabetes

Diagnostic testing for the major causes of monogenic diabetes is now widely available. Molecular genetic testing is traditionally guided by the clinical phenotype and also the relative prevalence of variants within that population. A good example of this approach is in people with a very specific clinical phenotype, where Sanger sequencing of the selected gene alone may be pragmatic, for example *GCK* testing in someone with fasting hyperglycaemia or *HNF1B* testing in a person with renal cysts and diabetes. However, for other types of monogenic diabetes, for example transcription factor MODY or neonatal diabetes, it may be difficult to predict the affected gene using clinical features alone. In the past this would have resulted in sequential testing of multiple genes, with associated delays in obtaining a diagnosis. Advances in DNA sequencing technologies now mean that panels of genes can be tested simultaneously using next-generation sequencing platforms without the considerable costs and time associated with earlier sequencing approaches [14, 25] and these are consequently replacing traditional single gene–targeted testing [26]. However, Sanger sequencing of a selected gene may still have value for specific individuals, for example *GCK* testing in a pregnant woman with mild fasting hyperglycaemia, in whom a rapid *GCK* test result would guide management of pregnancy.

Some caution is needed, as monogenic diabetes can occur in families that also have type 1 diabetes or type 2 diabetes. For similar reasons, the results of molecular genetic testing should be interpreted in the context of the clinical findings, for example a person with glucokinase diabetes could also develop type 1 or type 2 diabetes.

Where a family member has a confirmed genetic diagnosis, phenotypically unaffected relatives can be tested to assess whether they will be at risk of developing diabetes in the future. However, recommendations vary depending on the gene affected. In families with *GCK* MODY, screening of family members is not indicated as no follow-up or treatment is required. In *HNF1A* MODY families, annual urine testing for glycosuria in unaffected family members may be considered. In other types of monogenic diabetes, annual HbA_{1c} may be preferred to pre-symptomatic genetic testing, as even when a positive genetic test result is identified in a family member without diabetes it is not possible to accurately predict when the diabetes will develop. Where families request testing of members without diabetes, they should receive comprehensive genetic counselling on the potential benefits and disadvantages and be allowed to make their own decisions on the most appropriate option for them.

Glucokinase MODY

Glucokinase catalyses the phosphorylation of glucose to glucose-6-phosphate, the first and rate-limiting step in intracellular glucose metabolism in both β cells and hepatocytes (Figure 20.2). Owing to the unique catalytic properties of the enzyme, the rate of glucose phosphorylation is proportional to the glucose concentration, thus allowing β cells and hepatocytes to respond to changes in glycaemia. In the β cell, glucokinase acts as a glucose sensor, ensuring insulin release is appropriate to the glucose concentration [27]. Heterozygous loss-of-function variants in *GCK* result in a shift of the dose–response curve to the right [28]. Glycaemia is therefore regulated at a higher set-point, but remains tightly controlled. People with glucokinase variants are still able to stimulate their β cells maximally [28]. Glucokinase is also present in the liver and as a result these individuals have reduced hepatic glycogen synthesis [29]. Over 900 pathogenic variants have been identified that cause *GCK* MODY [30]. Homozygous loss-of-function glucokinase variants are a rare cause of insulin requiring diabetes presenting in the neonatal period [31]. Gain of-function variants cause congenital hyperinsulinism [32].

Clinical features

People with *GCK* MODY, due to heterozygous loss-of-function variants, have mild fasting hyperglycaemia from birth, usually 5.4–8.3 mmol/l (97–149 mg/dl), and HbA_{1c} results range between 40

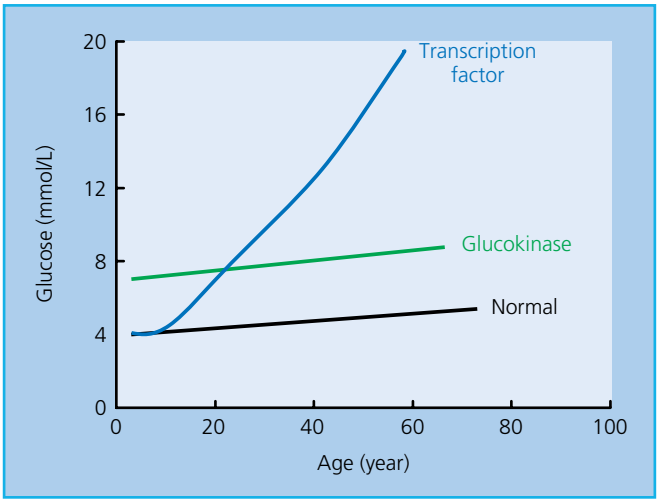

Figure 20.5 Variation of blood glucose concentration with age in people with glucokinase and transcription factor maturity-onset diabetes of the young. Source: Steele et al. [33] and Hattersley [35].

and 60 mmol/mol (5.8–7.6%) [33,34]. There is only a minor increase in HbA_{1c} with age, but this is also seen in older healthy people (Figure 20.5) [33, 34]. People with *GCK* MODY do not typically have symptoms of hyperglycaemia. Post-meal glucose values are only mildly raised and there is frequently only a small increase (<3 mmol/l in 70% [36] and <4.6 mmol/l in 90% [37] of those with *GCK* MODY) seen at two hours on an oral glucose tolerance test, which may explain the near-normal HbA_{1c} and rarity of complications [38, 39]. Glycated haemoglobin values above 60 mmol/mol (7.6%) would be suggestive of an alternative diagnosis and marked worsening of the glycaemia suggests the development of type 1 diabetes or type 2 diabetes in addition to *GCK* MODY. Microvascular and macrovascular complications are not seen, even when mild hyperglycaemia is present for 50 years [39]. Almost all individuals with *GCK* will have an affected parent; however, as glucokinase MODY is asymptomatic there may be no known family history of diabetes, despite its autosomal dominant inheritance. Testing of apparently unaffected parents can reveal that one parent has mildly raised fasting plasma glucose.

Differentiating from type 1 diabetes and 2 diabetes

Diagnosis of glucokinase MODY is most important in young individuals who may otherwise be thought to have type 1 diabetes and treated with insulin [40]. Unlike type 1 diabetes, hyperglycaemia remains mild and β-cell antibodies are expected to be negative; these individuals are only likely to be positive for antibodies in the same proportion as the normal population. Fasting C-peptide will remain detectable and the post-meal rise in glucose concentration will be far less than in type 1 diabetes. Differentiating glucokinase MODY from type 2 diabetes can be challenging, as both conditions can cause mild hyperglycaemia with a family history. Lack of obesity and absence of insulin resistance, a raised fasting glucose with a mild post-prandial rise, HbA_{1c} 40–60 mmol/mol (5.8–7.6%), and non-progression over time all suggest glucokinase MODY.

Management

Outside pregnancy, anti-diabetes medication is not recommended as hyperglycaemia is mild, significant microvascular complications are not seen, and medication does not lower glucose because the homeostatic regulation of glycaemia is preserved [41, 42]. Once diagnosis is confirmed, all diabetes treatment should be discontinued and no follow-up is required [34, 43]; however, this should be done with caution as it is possible for type 1 diabetes or type 2 diabetes to coexist with a *GCK* variant.

Glucokinase MODY and pregnancy

Clinical features

Women with *GCK* variants are frequently found to have hyperglycaemia during screening in pregnancy and represent 2% of white European women with gestational diabetes [12, 34, 44]. Their identification is important because they have a different clinical course than others with gestational diabetes. The birth weight of the newborn infant will depend on the variant status of both the mother and the fetus (Figure 20.6). Where only the mother carries the variant, maternal hyperglycaemia may result in increased fetal insulin secretion and growth, causing the fetus to be large for gestational age [45]. Infants that do not inherit the maternal *GCK* gene variation are at increased risk of macrosomia and its associated obstetric complications [46]. If the fetus inherits the variant from the father, however, birth weight is reduced by approximately 500 g as a result of reduced fetal insulin secretion and insulin-mediated fetal growth [45]. If both mother and fetus have the *GCK* variant, the two opposing effects are cancelled out and the newborn infant is of normal weight, provided that maternal blood glucose has been left untreated.

Genetic testing for *GCK* variants in pregnancy

We recommend testing for *GCK* variants when a pregnant woman is found to have persistently raised fasting plasma glucose, 5.4–8.3 mmol/l (97–149 mg/dl), both during or outside pregnancy. An absence of family history should not exclude the diagnosis, as asymptomatic hyperglycaemia in a parent may not have been detected. Genetic testing of women with a body mass index (BMI) <25 kg/m^2 and a fasting blood glucose >5.5 mmol/l (>100 mg/dl) has a sensitivity of 68% and on average 2.7 women will need to be tested to identify one case of *GCK* MODY [12].

Management

Women with hyperglycaemia resulting from glucokinase variants are often treated with insulin during pregnancy in an attempt to

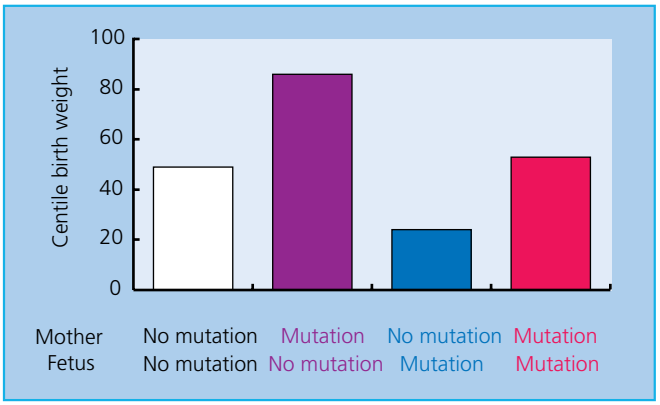

Figure 20.6 The centile birth weight of children in families with glucokinase variants. The weight is increased by the presence of a maternal variant and decreased by the presence of a fetal variant. Source: Data from Hattersley et al. [45].

correct the fasting hyperglycaemia. Fetal genotype, however, is a far greater determinant of fetal birth weight than maternal treatment and insulin appears to have little effect on fetal growth [46]. This probably reflects the difficulty in lowering the blood glucose in women with *GCK* MODY because of increased counter-regulation [47]. Women stop producing their own insulin and produce counter-regulatory hormones if blood glucose is reduced to normal levels, making successful control of blood glucose with insulin difficult. This results in frequent hypoglycaemic symptoms at non-hypoglycaemic blood glucose concentration and means that large doses of insulin may be required to reduce fasting hyperglycaemia to normal levels [47, 48]. In some cases where the fetus has inherited the variant, intensive insulin treatment has resulted in a low–birth weight child [48]. This is to be expected, as a small baby is seen when the fetus inherits a variant from the father and is born to a normoglycaemic mother [45, 49].

At present treatment decisions in glucokinase gestational diabetes are related to fetal growth as shown by ultrasound scans, rather than being made solely on maternal glycaemia [48]. If the abdominal circumference is greater than the 75th centile, insulin may be used, but early delivery is the most successful strategy [34]. Testing fetal genotype *in utero* is not without risk and is not recommended unless amniocentesis or chorionic villus sampling is being undertaken for an alternative reason [50]. However, assays to detect cell-free fetal DNA (cffDNA) in maternal serum have recently been developed to allow non-invasive fetal genotyping, which can be used to determine appropriate treatment for maternal hyperglycaemia and identify pregnancies at risk of macrosomia [51]. The test is highly sensitive and specific (86.8% and 100%, respectively [51]), with no reported false positives or false negatives. Further guidelines for the management of pregnancy in individuals with *GCK* variants are available at www.diabetesgenes.org.

HNF1A and *HNF4A* (Transcription factor MODY)

Transcription factors are proteins that bind to DNA and form part of a complex regulatory network controlling gene expression. The majority of people with MODY have a heterozygous variant in a transcription factor gene, by far the commonest being variants in the hepatic nuclear factors 1A and 4A (*HNF1A* and *HNF4A*). Diabetes resulting from variants in other transcription factor–encoding genes including *HNF1B* and insulin promoter factor 1 (IPF-1) are discussed elsewhere in this chapter.

Transcription factor variants alter insulin secretion in the mature β cell as well as altering β-cell development, proliferation, and cell death. Variants in the hepatic nuclear factors alter levels of proteins critical in metabolism, including the glucose transporter GLUT2 and key enzymes in the mitochondrial metabolism of glucose [52–54]. Reduced β-cell proliferation and preserved or increased apoptosis could explain the progressive deterioration in β-cell function seen in these individuals [54–57]. Variants in *HNF1A* account for up to 70 % of cases of MODY, with over 500 different variants reported [30]. In the UK, variants in *HNF4A* account for approximately 10 % of MODY cases [8].

Clinical features

Heterozygous transcription factor variants cause autosomal dominant diabetes presenting in adolescence or early adulthood resulting from progressive failure of insulin secretion. While diabetes is similar in *HNF1A* and *HNF4A* variant carriers, as a result of a common pattern of β-cell dysfunction, several differences in extra-pancreatic features occur (Table 20.3).

Diabetes

People with transcription factor MODY are usually born with normal glucose tolerance and then show progressive β-cell dysfunction until they develop diabetes, usually aged 10–30 years (Figure 20.5). Of *HNF1A* carriers, 63% are diagnosed with diabetes by the age of 25 years and 79% by the age of 35 years. The age of diagnosis is partly related to the location of the underlying variant within the gene [58–60]. The age of diagnosis is earlier in people with *HNF1A* than *HNF4A* [7]. Those who show deteriorating glycaemia with age require pharmacological treatment. In the oral glucose tolerance test in those with *HNF1A* MODY, in contrast to people with glucokinase variants, the fasting glucose is often normal initially, but there is marked elevation of glycaemia at two hours and consequently a large two-hour increment (>5.0 mmol/l; 90 mg/dl) [36]. This occurs because insulin secretion rates in early *HNF1A* MODY remain appropriate, with blood glucose values <8.0 mmol/l (145 mg/dl); however, when blood glucose levels rise above 8.0 mmol/l, the insulin secretion rates are reduced significantly in comparison to non-variant carriers without diabetes and result in a rise in blood glucose levels [61]. Microvascular complications are frequent particularly when hyperglycaemia is inadequately treated [62]. People with transcription factor MODY tend to be lean and insulin sensitive; obesity occurs at similar levels to the normal population.

Extra-pancreatic clinical features

These are summarized in Table 20.3 and discussed in more detail in the following.

HNF1A

People with *HNF1A* variants have elevated levels of high-density lipoprotein (HDL) cholesterol, which contrasts with the reduced HDL levels seen in type 2 diabetes [63]. Despite this, they have a greater risk of coronary heart disease than people with type 1 diabetes. Frequency of microvascular complications is similar to that seen in type 1 and type 2 diabetes and relates to glycaemic levels [62]. *HNF1A* variants are associated with a reduced renal threshold

Table 20.3 Extra-pancreatic features assisting in the differential diagnosis of transcription factor maturity-onset diabetes of the young (MODY).

Transcription factor	Extra-pancreatic clinical features
HNF1A	Low renal glucose threshold (glycosuria) Raised HDL cholesterol Raised cardiovascular risk (in excess of type 2 diabetes) Liver adenomas
HNF4A	Increased birth weight or macrosomia Neonatal hypoglycaemia Low HDL cholesterol, low lipoprotein A1 and A2, raised LDL cholesterol
HNF1B	Renal cysts and renal development disorders and multiple others. See Table 20.5
NeuroD1	None described

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

for glucose. Variant carriers without diabetes may develop glycosuria after a glucose challenge even if glycaemia remains within normal limits [64]. Individuals with *HNF1A* variants have a greater risk of liver adenomatosis and its complications, including acute intra-abdominal haemorrhage [65]. Screening for liver adenomas, in people with *HNF1A* variants with no clinical features suggesting adenomas, needs to be considered carefully, as there is no treatment that can be offered at present.

HNF4A

HNF4A variants are associated with an 800 g increase in birth weight compared with non-variant-carrying siblings [66]. This means that the offspring of *HNF4A* variant-carrying fathers, as well as the offspring of *HNF4A* mothers, are at risk of macrosomia. There is also an increased risk of hypoglycaemia in affected neonates. These features relate to increased insulin secretion *in utero* and in early infancy, which evolves into reduced insulin secretion and diabetes in later life [66]. Recently, cffDNA testing has become available to determine fetal genotype and aid the management of *HNF4A* pregnancies [51]. *HNF4A* variant carriers have reduced levels of HDL (and lipoprotein A1 and A2) and frequently have raised LDL cholesterol, while triglyceride levels are similar to population norms [67].

Differentiating from type 1 diabetes

Individuals with *HNF1A* or *HNF4A* MODY are frequently misdiagnosed as having type 1 diabetes as they have symptomatic diabetes presenting in adolescence or young adulthood. We recommend genetic testing by targeted next-generation sequencing to detect variants in *HNF1A/HNF4A* in any young adult with apparent type 1 diabetes, who is antibody negative to at least GAD and IA2 at diagnosis and also has a parent with diabetes. *HNF4A* should be suspected where there is increased birth weight and/or neonatal hypoglycaemia. Evidence of non-insulin dependence increases the likelihood of a positive result, shown by a non-fasting random C-peptide >200 pmol/l 3–5 years after diagnosis (i.e. outside the honeymoon period) [37].

Differentiating from type 2 diabetes

HNF1A/HNF4A should be suspected and targeted next-generation sequencing performed in people otherwise suspected to have type 2 diabetes where the following features are present ([37] and www.diabetesgenes.org):

- Young-onset diabetes: typically diagnosed before 25 years of age in at least one family member.
- Family history of diabetes: in at least two generations and ideally two individuals diagnosed in their 20s or 30s, particularly where affected individuals do not have obesity.
- Absence of obesity, acanthosis nigricans, or other evidence of insulin resistance.

In addition, marked sensitivity to sulfonylureas (hypoglycaemia on low doses) and a lipid profile showing normal or raised HDL cholesterol and normal or low triglycerides (atypical for type 2 diabetes) would all be supportive of a diagnosis of *HNF1A* rather than type 2 diabetes [63]. Individuals with *HNF4A* variants have a normal renal threshold for glucose, but frequently have a personal and/or family history of high birth weight and/or neonatal hypoglycaemia.

Management

People with both *HNF1A* and *HNF4A* variants are sensitive to sulfonylurea therapy, which is recommended as first-line treatment [67, 68]. Better glycaemic levels are often seen with sulfonylureas than with insulin and the fasting glucose–lowering effect is four times greater than that seen in type 2 diabetes [68, 69]. Transfer to sulfonylurea treatment is successful in the majority of people, although insulin therapy may be required as the duration of diabetes progresses [70]. Even very low doses of sulfonylurea may cause hypoglycaemia in individuals with *HNF1A/HNF4A* MODY. The starting dose of sulfonylurea should therefore be low, typically an initial dose of 20–40 mg/day gliclazide or 2.5 mg/day glibenclamide in adults. If there is hypoglycaemia with low doses of standard agents, a short-acting agent such as nateglinide may be appropriate [71]. Recent data from the UK UNITED study indicate that individuals with *HNF1A/HNF4A* MODY who were more likely to be successfully managed on sulfonylurea therapy alone had a shorter diabetes duration, lower HbA_{1c}, and lower BMI at the time of genetic testing [43]. However, individuals with *HNF1A/HNF4A* MODY with a longer duration of diabetes (>11 years), especially in those with overweight or obesity and who had a high HbA_{1c} at the time of genetic diagnosis, were more likely to require insulin treatment in addition to a sulfonylurea [43]. Glucagon-like peptide 1 (GLP-1) receptor agonists are also effective at reducing glycaemia [72]. When sulfonylureas are not controlling hyperglycaemia, sodium-glucose cotransporter-2 (SGLT-2) inhibitors can improve glycaemic levels, but may result in marked hypovolaemia due to excessive urinary glucose loss. More research is required to assess the safety and efficacy of SGLT-2 inhibitors in individuals with *HNF1A* MODY, who have a low renal threshold for glucose due to reduced SGLT2 activity. Recently, the DPP-4 inhibitor linagliptin was shown to be an effective add-on treatment to the sulfonylurea glimepiride in individuals with *HNF1A* variants by improving glycaemic variability and HbA_{1c}, without increasing the risk of hypoglycaemia [73]. Due to the increased risk of cardiovascular disease in *HNF1A*, statin therapy should be recommended for those aged over 40 years.

Management in pregnancy

Evidence to support management strategies for *HNF1A* and *HNF4A* in pregnancy is limited, but there is a 50% chance that the fetus of an affected parent will inherit the variant. The sulfonylurea glibenclamide has been widely used for treatment of gestational diabetes; however, glibenclamide crosses the placenta [74, 75] and stimulates fetal insulin secretion, resulting in an increased risk of macrosomia and neonatal hypoglycaemia [76, 77]. Due to the risk of stimulating fetal insulin secretion, women with *HNF1A/HNF4A* variants treated with sulfonylurea prior to conception with good glycaemic levels should either transfer to insulin before conception, at the risk of a brief increase in glycaemic levels, or continue with glibenclamide treatment in the first trimester and transfer to insulin in the second trimester [78]. In women with *HNF1A/HNF4A* MODY, glibenclamide should be avoided during the third trimester to avoid increased fetal weight gain [78].

Special considerations in *HNF4A* pregnancies

If a fetus carries the affected *HNF4A* gene, the risk of macrosomia and neonatal hypoglycaemia is extremely high whether the variant is inherited from the mother or father [66], as it will add >800 g to the birth weight, which may result in considerable obstetric complications. Early delivery should be considered when the fetus inherits a *HNF4A* variant from either parent [78]. In women with *HNF4A*, there is an additional contribution to fetal birth weight from maternal glycaemia and it is very important to avoid adding to this further by refraining from sulfonylurea (glibenclamide) treatment from the second trimester onwards.

Recent developments in non-invasive prenatal testing to detect cffDNA in maternal blood will enable personalized management of pregnancies based on the fetal genotype and identify pregnancies at increased risk of macrosomia [51] due to *HNF4A* variants. Further guidelines for the management of pregnancy in individuals with *HNF4A* variants are available at www.diabetesgenes.org.

Rare subtypes of MODY

Two rare subtypes of MODY are *ABCC8* [79] and *KCNJ11* [80] and are important to recognize, as affected individuals can be successfully treated with sulfonylureas. The variants in *ABCC8* and *KCNJ11* that cause MODY can, but do not always, present as transient neonatal diabetes mellitus and are discussed shortly.

Transcription factor variants very rarely causing autosomal dominant β-cell diabetes have been identified in the genes *IPF1* [81], *NEUROD1* [82–84] and *RFX6* [7]. These genes often only cause a MODY-like phenotype when there are severe protein-truncating variants with reduced penetrance [7, 82]. The rarity of these cases and reduced penetrance mean that no information has been published on how these individuals should be optimally managed. Variants in *KLF11*, *PAX4*, and *BLK* were previously suggested as causal genes, but are now known not to cause MODY and therefore should not be tested.

Neonatal diabetes and diabetes diagnosed within six months of life

Individuals diagnosed with diabetes within the first six months of life (referred to as neonatal diabetes) are likely to have monogenic diabetes and not type 1 diabetes [85–88]. These individuals usually present with ketoacidosis and absent or very low C-peptide. Neonatal diabetes is rare, affecting 1 in 100 000 live births [89, 90]. Approximately half of cases remit spontaneously and are therefore termed transient neonatal diabetes mellitus (TNDM), as opposed to permanent neonatal diabetes mellitus (PNDM) where diabetes persists [91]. TNDM often recurs in later life after the initial remission [93]. Neonatal diabetes results from variants of key genes involved in β-cell development or function [14]. Table 20.4 summarizes the known genetic causes of neonatal diabetes.

Permanent neonatal diabetes

Approximately half of PNDM is caused by variants in the genes *KCNJ11* and *ABCC8*, which encode the Kir6.2 and SUR1 subunits, respectively, of the β-cell adenosine triphosphate (ATP)-sensitive potassium channel (K_{ATP} channel) [79, 80, 97–99]. This channel is constitutively open and regulates insulin secretion by closing in response to the raised intracellular ATP levels that occur as a consequence of hyperglycaemia. Channel closure triggers depolarization of the β-cell membrane, which leads to insulin secretion. Activating variants in *KCNJ11* and *ABCC8* prevent closure of the potassium channel in response to increased ATP, so the β cell remains hyperpolarized and unable to secrete insulin [100]. Sulfonylureas close the β-cell K_{ATP} channel by an ATP-independent route and have been used successfully in the management of individuals with neonatal diabetes resulting from *KCNJ11* and *ABCC8* variants [101]. In offspring of unrelated parents the majority of PNDM resulting from K_{ATP} channel variants arise spontaneously from *de novo* heterozygous variants. The remaining cases are inherited mainly in an autosomal dominant pattern [99].

The K_{ATP} channel is also present in the brain, nerves, and muscles. Reflecting this distribution of channels, 20% of children with *KCNJ11* variants (and occasionally those with *ABCC8* variants) have severe neurological features [80, 88, 97, 100]. Recent data suggest that after thorough assessment the rate of psychological and neurological features is much higher in both *KCNJ11* and *ABCC8* PNDM than previously suggested [102, 103]. In-depth testing of 27 individuals with K_{ATP} channel gene variants (*KCNJ11* and *ABCC8*) found that all the participants had neuropsychological dysfunction [102]. In long-term follow-up studies, neurological features were found to persist into adulthood in all *KCNJ11* participants [104, 105]. In individuals with *ABCC8*-related PNDM, 62% had persistent, long-term psychiatric or neurological features [103].

Heterozygous variants in the insulin gene (*INS*) have been identified in ~12% of cases of isolated PNDM and insulin treatment is required [106, 107]. Other genetic causes appear to be relatively rare [14, 108], as outlined in Table 20.4. Parental consanguinity is more likely to result in autosomal recessive inheritance [14]. In children born to consanguineous parents, the commonest cause of PNDM is a homozygous variant in the *EIF2AK3* gene, causing Wolcott–Rallison syndrome [14].

Clinical features

Diabetes caused by *KCNJ11* variants typically present in the first 26 weeks of life (median 4–6 weeks) with marked hyperglycaemia often accompanied by ketosis. C-peptide is usually undetectable and pancreatic auto-antibodies negative [80]. As with all neonatal diabetes subtypes, infants are often small for gestational age as a result of reduced fetal insulin secretion with consequent decreased insulin-mediated growth.

Neonatal diabetes caused by an *ABCC8* variant has a similar phenotype but leads to TNDM more commonly than PNDM [97–99]. Children with neonatal diabetes due to *INS* variants present at a median age of 9 weeks and are also often small for gestational age, but do not have extra-pancreatic features [106].

The most common neurological features identified in individuals with PNDM resulting from *KCNJ11* and *ABCC8* variants are developmental delay and learning difficulties [103, 104]. Neurological features persist into adulthood, despite sulfonylurea therapy [103, 104], as a result of the limited function of the K_{ATP} channel in the brain and not as a consequence of long-standing diabetes [104]. The most severe form where neonatal diabetes is accompanied by developmental delay and epilepsy has been named developmental delay, epilepsy, and neonatal diabetes (DEND). *Intermediate DEND* (iDEND) refers to neonatal diabetes with less severe developmental delay and no epilepsy. The severity of the clinical condition relates closely to the underlying variant and its effect on K_{ATP} channel ATP sensitivity [100, 109].

Management

Although insulin therapy is commonly used in the initial period after diagnosis, the majority of those with *KCNJ11* and *ABCC8* variants can successfully transfer from insulin to sulfonylurea therapy, usually with significant improvements in glycaemic levels [98, 101]. Of those with *KCNJ11* variants 90% can discontinue insulin, while HbA_{1c} appears to improve in all, with a mean drop from 65 to 46 mmol/mol (8.1% to 6.4%) after 12 weeks [101]. Glibenclamide was initially chosen as it is non-selective and widely available; it has been used in the

Table 20.4 Causes of neonatal diabetes.

Pancreatic pathophysiology	Protein, chromosome, or gene affected	Inheritance	Phenotype
Reduced β-cell function	*KCNJ11*	Autosomal dominant (often *de novo*)	Permanent or transient neonatal diabetes and DEND syndrome
	ABCC8	Autosomal dominant or recessive	Permanent or transient neonatal diabetes and DEND syndrome
	Glucokinase (homozygous for variant)	Autosomal recessive	Isolated permanent neonatal diabetes. Both parents have heterozygous glucokinase associated hyperglycaemia
	SLC2A2	Autosomal recessive	Fanconi-Bickel syndrome: permanent neonatal diabetes, hypergalactosaemia, and liver dysfunction
	SLC19A2	Autosomal recessive	Roger syndrome: permanent neonatal diabetes, thiamine-responsive megaloblastic anaemia, and sensorineural deafness
Abnormal pancreatic development	Chromosome 6q24	Variable	Transient neonatal diabetes, macroglossia, and umbilical hernia
	GATA6	Autosomal dominant	Permanent neonatal diabetes, pancreatic agenesis, congenital heart defects, and biliary abnormalities
	PTF1A	Autosomal recessive	Permanent neonatal diabetes, pancreatic and cerebellar agenesis
	ZFP57	Autosomal recessive	Syndromic transient neonatal diabetes
	GLIS3	Autosomal recessive	Permanent neonatal diabetes, congenital hypothyroidism, glaucoma, liver fibrosis, developmental delay, and cystic kidney disease
	PDX1	Autosomal recessive	Permanent neonatal diabetes and pancreatic agenesis
	GATA4	Autosomal dominant	Permanent neonatal diabetes, pancreatic agenesis, and congenital heart defects
	NEUROD1	Autosomal recessive	Permanent neonatal diabetes, cerebellar hypoplasia visual impairments, and deafness
	NEUROG3	Autosomal recessive	Permanent neonatal diabetes with enteric anendocrinosis
Abnormal pancreatic development	*NKX2-2*	Autosomal recessive	Permanent neonatal diabetes, developmental delay, short stature, hypotonia, deafness, and constipation
	RFX6	Autosomal recessive	Permanent neonatal diabetes, intestinal atresia, and hepatobiliary abnormalities
	MNX1	Autosomal recessive	Permanent neonatal diabetes, developmental delay, and sacral agenesis
	HNF1B	Autosomal dominant	Transient neonatal diabetes, exocrine pancreas insufficiency, and renal cysts
Increased β-cell destruction	*INS*	Autosomal dominant	Isolated permanent neonatal diabetes
	EIF2AK3	Autosomal recessive	Wolcott–Rallison syndrome: permanent neonatal diabetes, skeletal dysplasia, and recurrent liver dysfunction
	FOXP3	X-linked	IPEX syndrome: autoimmune enteropathy, eczema, autoimmune hypothyroidism, and elevated immunoglobulin (Ig)E
	IER3IP1	Autosomal recessive	Permanent neonatal diabetes with microcephaly, simplified gyral pattern, and epilepsy
	WFS1	Autosomal dominant or recessive	Wolfram syndrome (recessive), isolated adult-onset diabetes (dominant), neonatal/infancy-onset diabetes, congenital sensorineural deafness, and congenital cataracts (dominant *de novo*)
	STAT3	Autosomal dominant	Early-onset polyautoimmunity including neonatal/early-onset diabetes, short stature, autoimmune-driven thyroid disease, enteropathy, and eczema
	IL2RA	Autosomal recessive	Permanent neonatal diabetes and additional autoimmune features
	LRBA	Autosomal recessive	Permanent neonatal diabetes and additional autoimmune features
	EIF2B1	Autosomal dominant	Permanent neonatal diabetes and transient liver dysfunction
	Trisomy of chromosome 21	Usually isolated cases	Permanent neonatal diabetes and Down's syndrome

DEND, developmental delay, epilepsy, and neonatal diabetes.
Source: Adapted from De Franco [93], Johnson et al. [94], De Franco et al. [95], and Rubio-Cabezas and Ellard [96].

majority of cases and may be more effective than other sulfonylurea agents [110]. The doses needed are often higher than those needed for the treatment of type 2 diabetes: a median dose of 0.45 mg/kg/day is required, with doses up to 1.5 mg/kg/day [101, 111]. Doses up to 2 mg/kg/day have been reported [112], but doses of 1 mg/kg/day or less are usually sufficient. Reports of side effects are mild and comprise transient gastrointestinal disturbances, the most common being diarrhoea, and tooth discoloration [105]. In individuals with PNDM caused by *KCNJ11* and *ABCC8* variants, sulfonylurea therapy is a safe and effective long-term treatment, maintaining excellent glycaemic levels for over 10 years without severe hypoglycaemia or serious side effects, even in high doses [103, 105]. Initiation of sulfonylurea therapy immediately after *KNCJ11* or *ABCC8* variants are confirmed appears to improve neurological outcomes [113] and sulfonylurea therapy may result in some improvement in neurological features, particularly in higher doses [103, 105, 110, 114, 115]. Earlier age at initiation of sulfonylurea therapy, ideally in the first six months of life, appears to correlate with better dose response [116]. Further information on transferring these individuals from insulin to sulfonylureas can be found at www.diabetesgenes.org. Neonatal diabetes resulting from *INS* variants requires insulin treatment [106].

Affected individuals with a heterozygous *KCNJ11* or *ABCC8* variant contemplating parenthood should be counselled that they have a 50% chance of passing on the variant to their offspring. Where unaffected parents, with a child affected by a heterozygous variant, are planning further pregnancies, the risk of further affected children is low because the possibility of a germline variant is approximately 5–10% [117]. Where parents have a child with neonatal diabetes caused by a recessive *ABCC8* variant, there is a 25% chance of each further offspring being affected, but the risk is low for subsequent generations. In pregnancy, if the fetus inherits a K_{ATP} neonatal diabetes variant (*KCNJ11* or *ABCC8*) from their mother, fetal insulin secretion will be greatly reduced *in utero*, resulting in reduced fetal growth by ~900 g [78, 80, 88, 118]. If the fetus and the mother both have K_{ATP} neonatal diabetes, maternal glibenclamide treatment is recommended as it will cross the placenta and provide *in utero* treatment to the affected fetus and normalize fetal growth. If the fetus is unaffected, maternal glibenclamide treatment is not recommended in the third trimester as it will exacerbate neonatal hypoglycaemia and excessive fetal growth [78, 119]. Awareness of fetal genotype through the use of cffDNA testing is an important addition to guide management of K_{ATP} neonatal diabetes pregnancies [51].

Transient neonatal diabetes

The genetic aetiology of more than 90% of TNDM has been established. The majority (70%) of cases result from abnormalities in the q24 region of chromosome 6 (6q24) affecting imprinted genes [92, 120]. Genetic imprinting occurs when only the maternally or paternally inherited allele of a gene is expressed and this is usually controlled by methylation. In TNDM paternal uniparental disomy, paternal duplication of 6q24 or abnormal methylation of the maternal copy of the chromosome causes overexpression of the paternal copies of the genes *PLAGL1* (also known as *ZAC*) and *HYMAI* [120, 121]. Paternal duplication of 6q24 can be inherited, therefore this abnormality causes the majority of inherited TNDM cases. Uniparental disomy causes sporadic TNDM; cases resulting from abnormal methylation of the maternal copy of chromosome 6 may be sporadic or inherited [120, 121]. The majority (90%) of TNDM not associated with 6q24 abnormalities are caused by variants in *KCNJ11* and *ABCC8* [14, 88, 92, 98, 122, 123].

Clinical features

6q24 diabetes usually presents in the first week of life, often with severe hyperglycaemia and dehydration but usually without ketosis. Pancreatic auto-antibodies are usually negative and C-peptide is low or negligible. Low birth weight is common (mean birth weight approximately 2.0 kg), and there may be associated macroglossia and/or umbilical hernia [124]. Insulin treatment is required for a median of 12 weeks before the child goes into remission [120]. Diabetes recurs later in life, with an average age of recurrence of 14 years in approximately 50% as a result of β-cell dysfunction [120]. In some cases, hyperglycaemia may be intermittent and seen only at times of stress [120, 125]. Where TNDM is caused by *KCNJ11* and *ABCC8* variants, diabetes tends to present later (median 4 weeks), takes longer to remit, and is associated with less intrauterine growth restriction (median birth weight 2.6 kg) [92]. Importantly, in *KCNJ11*- and *ABCC8*-related TNDM individuals may not present in the neonatal period and may only present in the relapse phase in adolescence or young adulthood [92], usually with a dominant family history, and they are sulfonylurea sensitive.

Management

Insulin is required in the neonatal period for all cases initially, whereas treatment following relapse varies from diet to oral antidiabetes agents or insulin [125]. In TNDM cases resulting from *KCNJ11* and *ABCC8* variants, diabetes may be successfully managed with sulfonylureas [92, 98]. The best treatment options for 6q24-related TNDM following relapse remain unclear; however, recent data indicate that non-insulin-based therapies, including sulfonylureas, may be effective [126, 127].

Genetic counselling depends on the underlying genetic aetiology. Cases caused by uniparental disomy are sporadic and therefore have low risk of occurrence in either siblings or offspring of the affected child. Methylation defects often result from homozygous variants in the transcription factor gene *ZFP57* and therefore may be inherited in an autosomal recessive manner [121]. Offspring of men with 6q24 duplication have a 50% chance of developing TNDM, whereas if the abnormality is inherited from the mother they will not be affected because both maternal copies would be inactive due to methylation; however, the TNDM may occur in the following generation [125, 128].

Genetic testing in neonatal diabetes

At the time of diagnosis of neonatal diabetes it is unknown whether the diabetes will be transient or permanent. We recommend urgent Sanger testing for the most common causes of neonatal diabetes (*KCNJ11*, *ABCC8*, and *INS* variants) at diagnosis in all cases where diabetes is diagnosed before 6 months of age and if possible those between 6 and 9 months. Identifying variants in these genes is important as it will influence treatment. If a variant is not identified, we recommend testing for all known neonatal diabetes genes by targeted next-generation sequencing. An early diagnosis and very low birth weight make 6q24 most likely. A genetic cause (*KCNJ11* or *INS*) can be established in ~7% of diabetes diagnosed between 6 months and 1 year of age and so consideration should be given to testing this age group, especially where autoantibody tests are negative [87]. Novel screening methods to identify neonatal diabetes early have recently been developed, including utilizing dried blood spot cards to measure glucose, which can detect hyperglycaemia and

neonatal diabetes on day 5 of life [129]. Genetic testing for neonatal diabetes is provided for any individual diagnosed before 9 months of age anywhere in the world through the Genomics Laboratory at the Royal Devon and Exeter Foundation Trust. Details are available at www.diabetesgenes.org.

Diabetes with extra-pancreatic features

Several monogenic causes of diabetes are associated with distinct features occurring outside the pancreas. In many cases extra-pancreatic disease may be the presenting feature, for example in cystic fibrosis and haemochromatosis (Chapter 23).

Maternally inherited diabetes and deafness

Maternally inherited diabetes and deafness (MIDD) results from a variant in mitochondrial DNA and causes maternally inherited diabetes with bilateral sensorineural deafness that may be accompanied by a wide range of other features. It affects up to 1% of those with diabetes, but is frequently misdiagnosed [130].

Pathogenesis and inheritance

The vast majority of mitochondrial diabetes results from the m.3243A>G point variant in mitochondrial DNA and other mitochondrial DNA variants are rare [131]. The m.3243A>G variant affects the mitochondrial respiratory chain and therefore results in cellular energy deficiency. Organs with high metabolic activity including the endocrine pancreas and cochlea are most affected. Mitochondrial dysfunction in pancreatic islets results in abnormal β-cell function, loss of β-cell mass, and insulin deficiency [130]. As mitochondria are inherited from the mother, only the maternal line in a family is affected, and children of an affected father are not at risk. All children of an affected woman will inherit the variant; however, phenotype varies widely within a family due to heteroplasmy. Offspring inherit a mix of variant and wild-type mitochondrial DNA and the proportion of mitochondria carrying the variant will vary, as will segregation of variant and wild-type mitochondria to different tissues [132].

Clinical features

The characteristic clinical features of MIDD are summarized in Figure 20.7. The majority of variant carriers develop diabetes

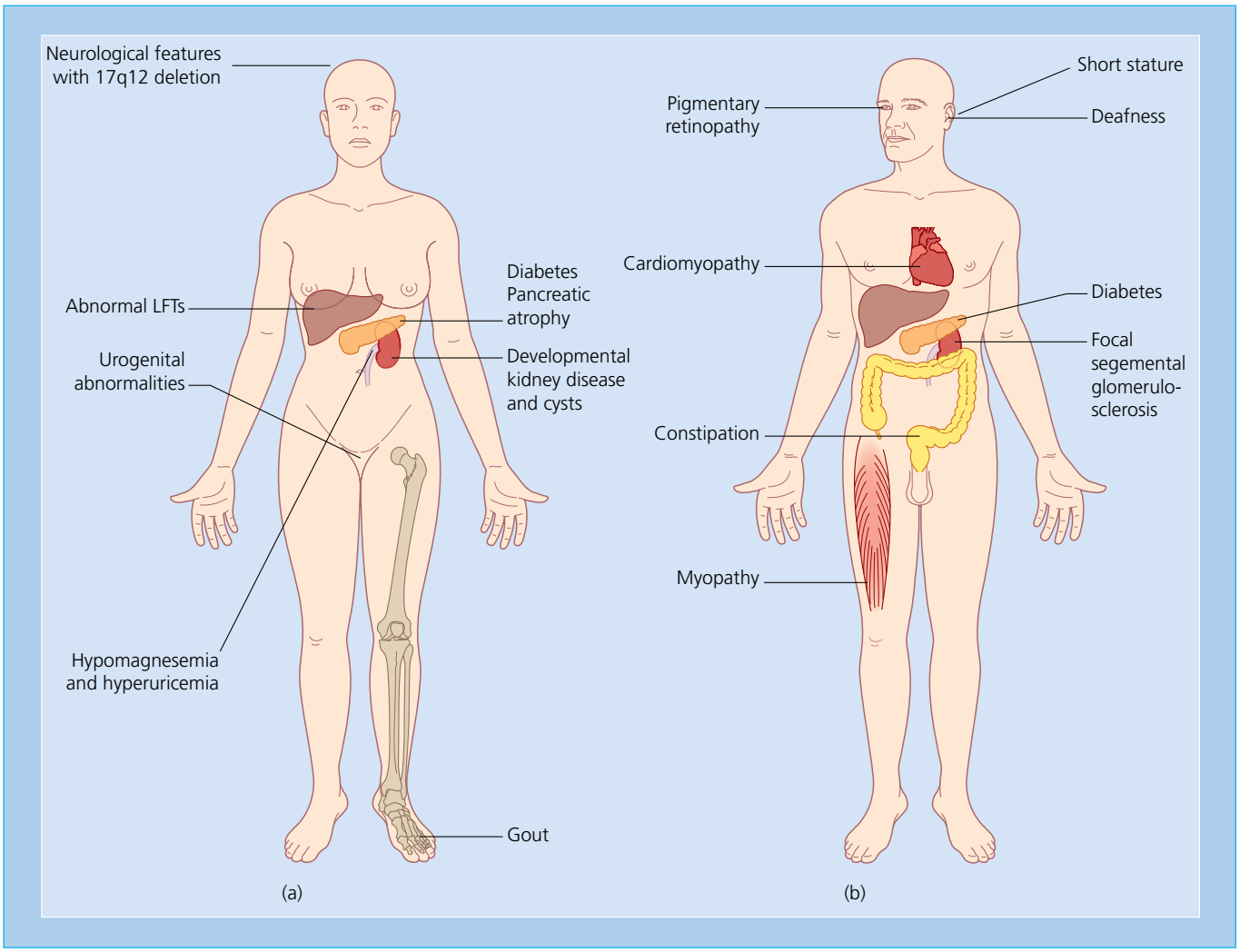

Figure 20.7 Phenotypes of (a) renal cysts and diabetes syndrome due to *HNF1B* variant or deletion; and (b) maternally inherited diabetes and deafness caused by mitochondrial m.3243A>G variant. LFTs, liver function tests. Source: Adapted from Murphy et al. [130] and Clissold et al. [150].

(over 85%) and sensorineural hearing loss (over 75%) [132–136]. Diabetes is progressive but may present acutely, with ketoacidosis occurring in ~8% of cases [132, 133, 137]. Mean age at diagnosis of diabetes is 37 years, but age of diagnosis can range from 11 years to 68 years [133, 137, 138].

Hearing loss typically develops in early adulthood and is more common in men than women [133, 135]. Those with the m.3243A>G variant have a high prevalence of renal failure, with focal segmental glomerular sclerosis found frequently on biopsy [133, 139]. Macular retinal dystrophy is a frequent finding, but rarely causes visual symptoms [130, 133, 139]. Cardiac abnormalities include left ventricular hypertrophy, heart failure, and cardiac arrhythmias [140–143]. Other clinical manifestations of the m.3243A>G variant include short stature, MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes), psychiatric disorders, proximal myopathy, and gastrointestinal symptoms, particularly constipation [130].

Differentiating from type 1 diabetes and type 2 diabetes

Diabetes caused by the m.3243A>G variant is difficult to differentiate from type 1 diabetes or type 2 diabetes. The presence of deafness in the individual or clustering of diabetes and/or sensorineural deafness in maternal relatives should prompt investigation for the m.3243A>G variant. The diagnosis can be confirmed by testing for the m.3243A>G variant in blood leucocytes or urine. In rare cases the result may be negative on blood-derived DNA because of heteroplasmy loads in leucocytes. Urine or buccal samples may therefore be preferable [130].

Management

Insulin treatment is usually required within two years of diabetes diagnosis [132, 133, 137, 144]. There is a theoretical basis for avoiding metformin in view of the risk of lactic acidosis [130, 132]. Whether there is benefit for the diabetes from use of coenzyme Q10 supplementation is currently unclear [130, 145, 146]. Monitoring for cardiac manifestations should be considered from a young age. Aggressive blood pressure management and early angiotensin-converting enzyme (ACE) inhibitor treatment may be appropriate in view of the high risk of renal complications. Management of hearing loss involves avoidance of exacerbating factors, prompt treatment of ear infections, hearing aids if necessary, and consideration of cochlear implants where there is profound hearing loss [130, 147, 148].

Maternal relatives of affected individuals and children of a woman with the disease should be assumed to carry the m.3243A>G variant. Therefore, annual HbA_{1c} after 30 years and prompt referral to audiology if suspicion of hearing loss and complications of MIDD may be advisable.

Renal cysts and diabetes (*HNF1B* MODY)

HNF1B is a transcription factor with a role in regulating gene expression in a number of tissues including the pancreas, kidneys, liver, genital tract, and gut [149]. Heterozygous deletions or variants in *HNF1B* can cause developmental abnormalities in all these organs, although the commonest phenotypes are renal abnormalities and diabetes. Renal cysts and diabetes (RCAD) syndrome is used to describe the combination of diabetes and renal cysts related to *HNF1B* variants. *HNF1B* abnormalities may show autosomal dominant inheritance, although up to 50 % of cases arise spontaneously and there is a wide variation in phenotype even with identical variants [150, 151, 152–154].

Clinical features

The clinical features are summarized in Table 20.5 and Figure 20.7. Developmental renal disease is the most consistent feature, with renal cysts being the commonest manifestation [150]. Other possible renal abnormalities include glomerulocystic kidney disease, cystic renal dysplasia, and morphological abnormalities such as horseshoe or single kidney. Renal function can range from normal to dialysis dependent [156, 157]. The mean age of diagnosis of diabetes is 24 years, but the age of diagnosis can vary from infancy to over 60 years old [150]. Diabetes is usually associated with pancreatic hypoplasia and may be associated with exocrine dysfunction, although this can result in mild or moderate symptoms of malabsorption [158–160]. Low birth weight is common and very rarely transient neonatal diabetes has been described [159]. Other clinical manifestations include non-progressive abnormal liver function tests, genital tract malformations, hypomagnesaemia, hyperuricaemia, and familial hyperuricaemia nephropathy [158, 161]. Neurodevelopmental disorders including autism spectrum disorder are identified in ~40 % of individuals with an *HNF1B* whole-gene deletion occurring as part of a chromosome 17q12 microdeletion, but are not associated with *HNF1B* intragenic variants [155, 162]. Mild facial dysmorphic features are also suggestive of a 17q12 deletion and include high forehead, high arched eyebrows, long philtrum, long face, and anteverted nares [155]. An association with chromophobe renal cell carcinoma has been reported, reflecting a probable role for *HNF1B* as a tumour suppressor gene [163, 164].

Table 20.5 Features of people with *HNF1B* variants causing RCAD (renal cysts and diabetes) in a UK cohort.

Clinical features	Details
Renal phenotype	
Renal cysts	Common
Renal impairment	Common (15% require dialysis/ transplantation)
Morphological renal abnormalities	Occasional (Horseshoe or single kidney)
Renal histology (includes)	Glomerulocystic kidney disease, cystic renal dysplasia, oligomeganephronia
Hypomagnesaemia	44%, proximal tubular defect
Hyperuricaemia and gout	20% (clinical gout)
Diabetes	58%. Mean age of diagnosis 26 yr, range 0–61 yr
	Insulin treatment common
Other features	
Liver enzyme derangement	Mild, non-progressive
Subclinical exocrine pancreatic failure	Reduced faecal elastase (may require treatment)
Genital tract malformations	17%
Short stature	20% <2 SD below mean height
Neurodevelopmental disorders	Neuropsychiatric manifestations (autism in ~40% of those with whole-gene deletion)
Uncommon	Joint laxity, hearing loss, prognathism, pyloric stenosis, chromophobe renal cell carcinoma

SD, standard deviation.
Source: Adapted from Clissold et al. [150], Bingham and Hattersley [151], and Clissold et al. [155].

Differentiating from type 1 diabetes and type 2 diabetes
Approximately 50% of *HNF1B* variants and deletions are spontaneous and so there may be no family history. Testing for *HNF1B* abnormalities should be considered where there is unexplained cystic renal disease, glomerulocystic disease, or other renal developmental abnormalities with or without a past medical or family history of diabetes. It should also be considered in individuals with genital tract abnormalities associated with renal abnormalities. Both simple renal cysts and diabetes are common in the general population and should not lead to automatic testing for *HNF1B* abnormalities; testing would be considered when the diabetes is young onset and atypical for type 1 diabetes and type 2 diabetes. Testing for *HNF1B* should always include dosage analysis to detect gene deletions, as these are common and will be missed if the laboratory performs sequencing only [165].

Management
Although the majority of individuals with *HNF1B* variants will require insulin treatment [166], some individuals, soon after diagnosis, may be briefly managed with sulfonylurea therapy [167]. Renal management is similar to management of other chronic progressive renal diseases. Our recommendation is that adults with normal renal function should have their serum creatinine and estimated glomerular filtration rate (eGFR) repeated annually. Children with normal renal function should have their serum creatinine and eGFR checked every 2–3 years. All individuals should undergo a renal ultrasound scan to assess for structural anomalies. If initial imaging is abnormal, repeat renal ultrasound imaging every 3–5 years is recommended. If the initial ultrasound scan is unremarkable, we suggest repeating imaging every 3–5 years throughout childhood. In adults, monitoring renal function using serum creatinine and eGFR would be sufficient. Annual assessment of HbA_{1c} in adults without a diagnosis of diabetes is recommended. In children without a diagnosis of diabetes, annual urinalysis to test for glycosuria and monitoring HbA_{1c} when routine blood samples are being collected may be helpful. Faecal elastase should be tested to check for pancreatic insufficiency when there are gastrointestinal symptoms, as treatment with Creon® (AbbVie, North Chicago, IL, USA) may be required. Other tests that may be useful in diagnosis of *HNF1B* include liver function tests, serum magnesium, and serum urate.

Other monogenic β-cell diabetes with extra-pancreatic features

Wolfram syndrome
Wolfram syndrome is a rare autosomal recessive neurodegenerative disorder caused by biallelic variants in the *WFS1* gene, and rarely *CISD2*, and is characterized by diabetes insipidus, diabetes mellitus, optic atrophy, deafness (hence DIDMOAD syndrome), and a variety of central nervous system abnormalities. Consideration should be given to this diagnosis where there is a combination of diabetes and optic atrophy [168–170].

Thiamine-responsive megaloblastic anaemia syndrome
Thiamine-responsive megaloblastic anaemia (TRMA) syndrome is a rare autosomal recessive condition caused by variants in the *SLC19A2* gene and is characterized by megaloblastic anaemia (which may be mild), non-autoimmune diabetes, and sensorineural hearing loss [171]. Treatment with high-dose thiamine can improve some features, including diabetes [172].

Wolcott–Rallison syndrome
Wolcott–Rallison syndrome is a rare autosomal recessive condition caused by biallelic variants in *EIF2AK3* and is characterized by early-onset diabetes, spondyloepiphyseal dysplasia, and recurrent hepatic and/or renal dysfunction. Diabetes usually presents in infancy and requires insulin treatment [173].

Monogenic diabetes with pancreatic exocrine dysfunction
Variants in the carboxyl ester lipase (*CEL*) gene have been identified as a rare cause of monogenic diabetes with pancreatic exocrine dysfunction. Pancreatic exocrine dysfunction often occurs decades before development of diabetes and can be detected by low faecal elastase levels in early childhood [174, 175].

Primrose syndrome
Primrose syndrome is a rare condition caused by variants in the *ZBTB20* gene and is characterized by macrocephaly, intellectual disability, dysmorphic facial features, large calcified external ears, ectopic calcifications, progressive muscle wasting, and diabetes [176].

Insulin resistance

Monogenic causes of diabetes resulting from insulin resistance include the inherited lipodystrophies, variants affecting the insulin receptor or post-receptor signalling, and other monogenic syndromes associated with insulin resistance where abnormalities of insulin action are not the primary disorder. There can be considerable clinical overlap in clinical presentation between these conditions [177]. The key features of severe insulin resistance likely to be associated with a monogenic cause of diabetes are:
- The presence of acanthosis nigricans (Figure 20.8).
- Ovarian cysts, subfertility, and hyperandrogenism in women.
- Hyperinsulinaemia as evidenced by raised endogenous insulin levels, or in those on insulin treatment very high doses of exogenous insulin.

In a lean person, the presence of some or all of these features should prompt consideration of underlying monogenic causes of

Figure 20.8 Acanthosis nigricans affecting the neck of a 26-year-old woman with severe insulin resistance. Source: Reproduced with permission from Moller and O'Rahilly [178].

insulin resistance. While obesity does not exclude monogenic insulin resistance, it is very hard to detect on the background of obesity-related insulin resistance. The presence of other clinical features (Figure 20.9) is related to the underlying cause. Monogenic forms of insulin resistance are comprehensively reviewed elsewhere [179, 180].

Insulin receptor gene variants

Insulin exerts its effects through binding to a transmembrane receptor. Binding of insulin to the α-subunit of the receptor activates β-subunit tyrosine kinase activity, triggering protein activation cascades that lead to insulin's intracellular effects [181, 182]. Variants in the insulin receptor (*INSR*) gene lead to inherited insulin resistance syndromes. The severity of the resulting clinical phenotype depends on the extent of impairment of signal transduction resulting from the underlying variant [183].

Clinical features

Individuals with severe insulin resistance resulting from insulin receptor variants may have common features of severe insulin resistance, which include hyperinsulinaemia, acanthosis nigricans, ovarian hyperandrogenism, and disturbances of glucose homeostasis, which can include hypoglycaemia (classically post-prandial) as well as impaired glucose tolerance and diabetes [183]. However, they do not have features of ectopic fat, which is seen in lipodystrophy (see later). Three main syndromes resulting from insulin receptor variants leading to severe insulin resistance have been described:

- Type A insulin resistance syndrome/
- Rabson–Mendenhall syndrome.
- Donohue syndrome (previously known as leprechaunism).

These syndromes overlap and represent varying clinical features from a continuum of severity of receptor dysfunction rather than completely distinct syndromes [183]. Many individuals with insulin receptor defects and severe insulin resistance (men in particular) may not fit into the syndromic descriptions.

The commonest presentation is Type A insulin resistance syndrome, where individuals without obesity have severe insulin resistance, acanthosis nigricans, and hyperandrogenism. Affected females present in adolescence with polycystic ovarian disease, hirsutism, and signs of virilization (often termed HAIR-AN syndrome) [180, 184, 185]. Females have more prominent clinical features than males, with the majority of affected males remaining asymptomatic until they develop impaired glucose tolerance, usually in adulthood [180].

The syndromic types of insulin resistance seen with insulin receptor variants are rare and associated with more severe impairment of the insulin receptor function. Rabson–Mendenhall syndrome is an autosomal recessive disorder that presents in childhood with acanthosis nigricans, extreme growth restriction, dysplastic dentition, coarse facial features, lack of subcutaneous fat, pineal hyperplasia, and renal abnormalities including medullary sponge kidney and nephrocalcinosis [185–187]. Affected individuals may develop diabetes several years after diagnosis [188]. Most affected individuals do not survive puberty [185]. The most severe syndrome seen with insulin receptor variants is Donohue syndrome, a rare autosomal recessive disorder characterized by low birth weight, hirsutism, growth restriction, disordered glucose homeostasis, and characteristic dysmorphic features. Individuals usually do not survive infancy [185, 189].

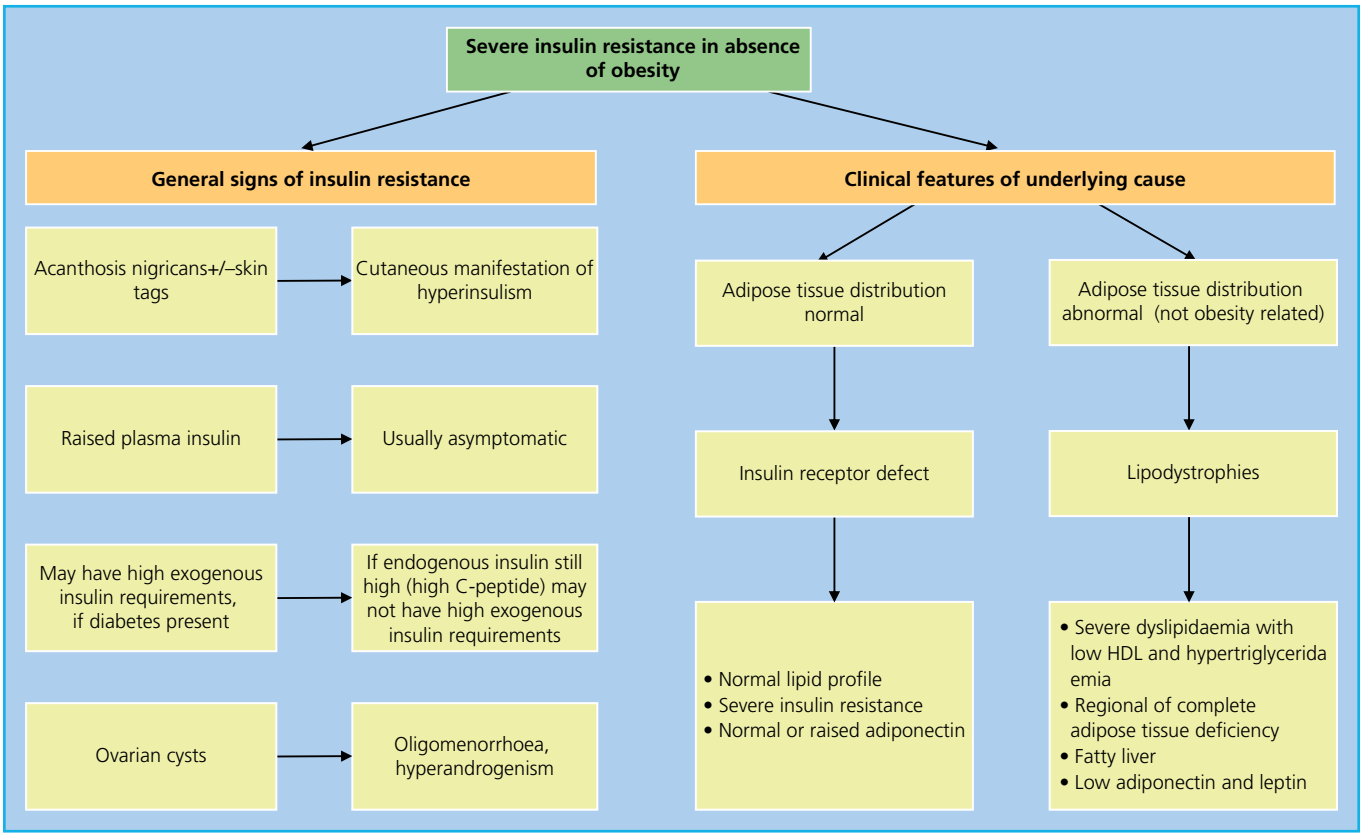

Figure 20.9 Features of monogenic severe insulin resistance. HDL, high-density liopoprotein.

Differentiating from type 1 diabetes and type 2 diabetes

The presence of features of insulin resistance in a slim individual is suggestive of an underlying insulin receptor gene variant. Serum adiponectin levels are typically high with insulin receptor variants, whereas they are low in other forms of insulin resistance. Adiponectin levels could be used as a screening test, with sequencing of the insulin receptor gene reserved for those cases where adiponectin levels are raised [177, 190, 191].

If the affected individual is on a high insulin dose (>3 units/kg/day), does not have obesity, and has elevated glycaemic indices, high non-fasting C-peptide levels can help discriminate insulin resistance from type 1 diabetes. Unlike type 2 diabetes and the lipodystrophies, triglyceride and HDL cholesterol levels are typically normal with insulin receptor variants [185].

Management

When the β cells of the person decompensate and diabetes develops with marked hyperglycaemia, treatment is difficult. While insulin sensitizers, such as metformin and thiazolidinediones, have a role in management, their effect is often limited and insulin therapy is required as β-cell function declines [185]. Glucose levels often remain high despite very large doses of insulin (often in excess of 500 units/day). U500 insulin has a role in reducing the insulin volumes required [185, 192]. Insulin pumps should be considered when very high doses of insulin are required.

Inherited lipodystrophies

Lipodystrophies are rare clinically heterogeneous disorders that are characterized by the selective loss of adipose tissue and accumulation of ectopic fat. They are associated with insulin resistance and other features such as diabetes, acanthosis, dyslipidaemia, hepatic steatosis, and (in women) hyperandrogenism, oligomenorrhoea, and polycystic ovaries [193]. Lipodystrophies may be inherited or acquired.

Familial partial lipodystrophy

Familial partial lipodystrophies are autosomal dominant disorders where insulin resistance in a slim person is associated with the loss of peripheral subcutaneous fat, resulting in ectopic fat. The two main subtypes result from variants in *LMNA* and *PPARG*.

The clinical features of familial partial lipodystrophy are a combination of the features of insulin resistance (acanthosis nigricans, hyperinsulinaemia, polycystic ovarian syndrome, virilization), direct features of lipodystrophy, and indirect features resulting from ectopic fat. Familial partial lipodystrophy associated with *LMNA* variants (also known as Dunnigan lipodystrophy) results in gradual peripheral subcutaneous fat loss from puberty [194, 195]. This, and the associated muscle hypertrophy, gives a muscular appearance of the arms and legs (Figure 20.10). There may be fat loss from the anterior abdomen and chest and excess fat deposition in the face, neck, and intra-abdominally [196, 197]. Ectopic fat accumulates in the liver, muscle, pancreas, and vasculature, resulting in the abnormal metabolism of glucose and lipids [198]. Diabetes is common, particularly in women, and appears in late adolescence or early adulthood [199]. Hypertriglyceridaemia may be marked and associated with pancreatitis. Elevated triglyceride levels and very low HDL cholesterol levels can aid in diagnosis. Cardiovascular mortality is high [200, 201].

Familial partial lipodystrophy associated with *PPARG* variants appears to be phenotypically similar to that caused by *LMNA* variants, although hypertension is more common [202, 203].

Figure 20.10 Familial partial lipodystrophy in a 46-year-old woman. There is truncal and limb lipodystrophy, preserved facial and neck adipose tissue, muscle hypertrophy, and acanthosis apparent in the groin regions.

Diagnosis may be obvious in women, but is more difficult in men where a muscular appearance of limbs is more usual. Early-onset diabetes in an individual without obesity and with acanthosis nigricans, low HDL cholesterol, and hypertriglyceridaemia should raise suspicion of lipodystrophy, particularly if there is marked peripheral fat loss [204]. Many individuals with lipodystrophy are mistakenly thought to have Cushing's syndrome.

Congenital generalized lipodystrophy (Berardinelli–Seip syndrome)

This is a rare (estimated prevalence 1 in 10 million) autosomal recessive disorder characterized by a near-complete absence of subcutaneous fat from birth, giving a muscular appearance [193]. Due to the absence of functioning adipocytes, lipids are stored in metabolically

active tissues. Those affected have features of severe insulin resistance, including often widespread acanthosis, hypertriglyceridaemia, and low HDL cholesterol [205]. Hepatic steatosis occurs early and may lead to cirrhosis; hepatomegaly is seen frequently [206–208]. Childhood growth is accelerated and bone age advanced. Diabetes commonly develops during adolescence. Other associated features include acromegaloid features, hypertrophic cardiomyopathy, skeletal muscle hypertrophy, bone cysts, and intellectual impairment [208]. Serum leptin and adiponectin levels are markedly reduced [209].

Four molecularly distinct forms of congenital generalized lipodystrophy have been identified: type 1 (*AGPAT2* variants); type 2 (*BSCL2* variants); type 3 (*CAV1* variants); and type 4 (*PTRF* variants) [193, 210–212]. *AGPAT2* and *BSCL2* account for the majority of cases and have some difference in phenotype. Some people with this phenotype do not have variants in any of these genes and so it is likely there are further genetic aetiologies to be discovered.

Mandibular hypoplasia, deafness, progeroid features, and lipodystrophy (MDPL) syndrome

MDPL syndrome is an extremely rare autosomal dominant condition caused by variants in the *POLD1* gene on chromosome 19 and is characterized by lipodystrophy, dysmorphic facial features, sensorineural deafness, and metabolic abnormalities including severe insulin resistance and diabetes [213, 214]. In those with diabetes, we recommend using metformin in doses of at least 2 g/d, as this decreases insulin resistance and improves insulin sensitivity.

Other inherited monogenic forms of lipodystrophy

Other inherited subtypes of lipodystrophy associated with dysmorphic features have now had genes discovered, including mandibuloacral dysplasia (*LMNA, ZMPSTE24*), SHORT syndrome (*PIK3R1*), neonatal progeroid syndrome (*FBN1, CAV1*), atypical progeroid syndrome (*LMNA*), and Keppen-Lubinsky syndrome (*KCNJ6*) [184, 215].

Management of lipodystrophy

Management should address insulin resistance, the main causes of morbidity and mortality, diabetes, cardiovascular and cerebrovascular disease, recurrent pancreatitis (as a result of severe hypertriglyceridaemia), cirrhosis, and psychological distress related to appearance [193]. The key point of management is to treat the ectopic fat. Despite being slim, these individuals have the same problems from ectopic fat as those with morbid obesity and so there are considerable parallels in the management of these two very different groups. The reduction in ectopic fat will result in reduced insulin resistance, reduced hyperglycaemia, lower blood pressure, more favourable lipid profile (lower triglycerides and higher HDL cholesterol), and reduced cardiovascular risk. To reduce ectopic fat the key aim is to reduce oral food intake, which is difficult, but these individuals will see great benefit from even minimal reduction in caloric intake.

Lifestyle changes should include an extremely low-fat diet (<15% total energy from fat) and low caloric intake. Reduced oral intake will reduce ectopic fat, reducing insulin resistance and improving glycaemic levels. To help reduced oral intake, GLP-1 receptor agonists are helpful as they reduce gastric emptying [216]. Roux-en-Y gastric bypass surgery (RYGB) may also be considered in the management of lipodystrophy. RYGB improves glycaemic indices, enhances insulin sensitivity, and promotes weight loss in familial partial lipodystrophy [217, 218]. Hypertriglyceridaemia that does not respond to measures to reduce ectopic fat may require treatment with fibrates and possibly high doses of fish oils. Given the very high cardiovascular risk, high-dose statins should be used very early and certainly once reaching adult life.

Glycaemic management requires a combination of oral treatments and high-dose insulin in the majority of cases. Early treatment with metformin is commonly used to improve insulin sensitivity [204]. Thiazolidinediones (glitazones) are not recommended as they require normal adipocytes to work well and they can cause further accumulation of fat in the face and neck [179]. Where insulin is needed dose requirements may be very high and both insulin pumps that reduce insulin requirements and U500 insulin should be considered. Where proteinuric renal disease develops, the threshold for renal biopsy should be low as non-diabetic renal disease (e.g. membranoproliferative glomerulonephritis and focal segmental glomerulosclerosis) is increased in lipodystrophy, possibly because of reduced immunoregulatory function of adipocytes [219].

Levels of the adipocytokine leptin are markedly reduced in severe lipodystrophies. Leptin replacement has been associated with marked improvements in glycaemic levels, reduced liver steatosis, and hypertriglyceridaemia in generalized lipodystrophy, but its role is limited in partial lipodystrophy and given the cost of the therapy should only be considered when leptin levels are extremely low [220–222].

Other monogenic conditions associated with insulin resistance

Other monogenic conditions associated with insulin resistance either have marked obesity (e.g. Alström and Bardet–Biedl syndromes), neurological disease including myotonic dystrophy and Friedreich ataxia, or rapid aging (e.g. Werner syndrome) [223].

Conclusion

Monogenic diabetes results from single gene changes that affect β-cell function or insulin sensitivity. Correct diagnosis can help define prognosis and the best treatment and allow screening of family members. Diagnostic testing is now widely available and should be considered where presentation is atypical for type 1 diabetes or type 2 diabetes, where there is an autosomal dominant family history, where there are characteristic associated features, and in all cases where diabetes has been diagnosed within the first six months of life.

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21 Drug-Induced Diabetes

Charles D. Ponte[1] and Devra K. Dang[2]

[1] Robert C. Byrd Health Sciences Center, West Virginia University – Schools of Pharmacy and Medicine, One Medical Center Drive, Morgantown, WV, USA

[2] University of Connecticut School of Pharmacy, Storrs, CT, USA

Key points

- Many commonly prescribed medications can contribute to hyperglycaemia or cause overt diabetes in predisposed individuals.
- The main mechanism by which glucocorticoids cause hyperglycaemia is by reducing insulin sensitivity in the liver, skeletal muscle, and adipose tissue in a dose-dependent fashion.
- Second-generation antipsychotic use requires scheduled monitoring of glucose, lipids, blood pressure, and body mass index.
- Although combined oral contraceptives are associated with metabolic abnormalities, their use is still recommended for women with type 1 diabetes or type 2 diabetes without vascular complications and in women with a history of gestational diabetes.
- Postmenopausal women can safely take menopause hormone therapy without adversely affecting glucose homeostasis or triggering diabetes.
- Menopause hormone therapy has minimal impact on established type 1 diabetes or type 2 diabetes in postmenopausal women. Continued surveillance of glycaemia is prudent in these women and appropriate adjustments should be made to their anti-diabetes drug regimens as needed.
- Thiazide-diuretics can affect glucose homeostasis in a dose-dependent manner, but the effect appears to be modest. Maintaining normokalaemia is the best defence against this potential metabolic consequence of thiazide use.
- Whether β-blockers affect glucose homeostasis or contribute to the development of overt diabetes is inconclusive. β-blockers with vasodilating properties, such as carvedilol and nebivolol, are the preferred choices for people with diabetes or those at significant risk for diabetes, unless contraindicated by comorbidities such as asthma.
- Statins appear to increase insulin resistance and decrease insulin secretion, with small increases in glycated haemoglobin (HbA_{1c}) and fasting glucose.
- Hyperglycaemia and diabetes have been reported with protease inhibitors and some nucleoside reverse-transcriptase inhibitors (zidovudine, stavudine, and didanosine). The nucleoside reverse-transcriptase inhibitors can cause insulin resistance and promote lipodystrophy and pancreatitis.
- Fluoroquinolone-associated dysglycaemia appears to be much more common with gatifloxacin compared to levofloxacin. Hyperglycaemia tends to occur within 1–2 weeks of therapy initiation. Any changes in glycaemia can be managed with careful adjustment of the anti-diabetes regimen and continued blood glucose monitoring.
- The calcineurin inhibitors cyclosporine and tacrolimus are associated with post-transplant diabetes. Risk factors include older age, obesity, corticosteroid use, other-than-White ethnicity, hepatitis C, and genetic determinants.
- Diazoxide is a long-known cause of drug-induced hyperglycaemia and even diabetic ketoacidosis. Its hyperglycaemic effects have been purported to result from impaired insulin secretion, increased glucose production, and decreased peripheral glucose utilization. Evidence suggests that insulin secretagogues (including the incretin mimetics) may be the drugs of choice to manage this condition.
- Whenever possible, exposure to drugs that could affect glucose regulation or glucose levels should be limited. If a precipitant drug cannot be avoided, careful monitoring for the occurrence of hyperglycaemia is warranted. If a morbid event occurs, the dose should be reduced or the drug discontinued.

Drugs can have countless therapeutic benefits and can be lifesaving. However, the potential also exists for drugs to do great harm. Drug therapy can worsen an underlying disease state, resulting in therapeutic challenges for the clinician. Diabetes is one such example where various drugs can worsen glucose levels and even contribute to hypoglycaemic episodes. Importantly, numerous commonly used medications can also predispose the individual to the development of hyperglycaemia and even overt diabetes. Corticosteroids, second-generation antipsychotics (SGAs), diazoxide, statins, oral contraceptives, and niacin are just a few examples of drugs that have been associated with hyperglycaemia or drug-induced diabetes. Various mechanisms have been proposed for drug-induced hyperglycaemia, which include insulin resistance, decreased insulin secretion, decreased glucose uptake, pancreatitis, weight gain, and increased hepatic gluconeogenesis. Whatever the cause, the clinician should be ever vigilant to the potential for drug-induced dysglycaemia, taking into consideration individual and drug factors, and be prepared to manage its consequences in the appropriate manner.

This chapter will describe selected drug classes and individual drugs that have been associated with hyperglycaemia or overt diabetes.

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Table 21.1 Other medications that can induce hyperglycaemia.

Antidepressants
Gonadotropin-releasing hormone agonists
Fish oil
Growth hormone
Interferons
L-asparaginase
Mammalian target of rapamycin (mTOR) inhibitors (everolimus, sirolimus, temsirolimus)
Megesterol acetate
Niacin
Phenytoin
Rifampin
Ritodrine
Somatostatin analogues – most significant with pasireotide
Teprotummab-trbw
Terbutaline
Thalidomide
Tyrosine kinase inhibitors

Source: Based on Dang et al. 2018 [1]; Wilkins and Sambamoorthi 2011 [2]; Sivendran et al. 2014 [3]; Pan et al. 2011 [4]; Novartis 2015 [5].

Attention will be given to predisposing factors along with the attendant pathophysiological characteristics, utilizing the relevant literature and emerging evidence. The focus will be on medications that are commonly prescribed and those with clear and significant potential for the development of diabetes. Other medications that can induce hyperglycaemia are listed in Table 21.1 [1–5]. The chapter will conclude with a discussion of strategies to prevent and manage drug-induced dysglycaemia.

Glucocorticoids

Of all of the medications that can potentially induce hyperglycaemia, glucocorticoids are the drug class that most consistently leads to this effect. Glucocorticoids have been reported to increase blood glucose when administered via numerous routes. They most commonly induce hyperglycaemia when administered intravenously or orally, at supraphysiological doses because of the high bioavailability potential for these routes. They have also been reported to increase blood glucose when administered by the intra-articular and epidural routes [6, 7], and some, but not all, studies found that inhaled corticosteroid led to hyperglycaemia [8, 9]. A case–control study of a large primary care registry in the UK found no association between inhaled, injected, ophthalmic, or topical glucocorticoids with incident diabetes, but oral glucocorticoids are associated with up to 2% of cases of new-onset diabetes. The authors acknowledged the limitations of the database, which may have provided an underestimation of the risk [10]. Other cohort studies have reported that the odds ratio for glucocorticoids-induced new-onset diabetes ranges from 1.36 to 2.31 [11].

The main mechanism by which glucocorticoids cause hyperglycaemia is through reduction of insulin sensitivity in the liver, skeletal muscle, and adipocyte, by approximately 50–70%, which appears to be dose dependent [11–15]. Glucocorticoid administration leads to decreased glucose transport 4 (GLUT4) expression and migration, decreased glycogen synthesis, and increased hepatic gluconeogenesis [16]. Glucocorticoids also decrease insulin production and secretion [17, 18].

The most common clinical presentation of glucocorticoid-induced hyperglycaemia is a rise in blood glucose starting in mid-morning and continuing throughout the day until bedtime [19]. Therefore, this adverse drug reaction may not be detected if only the fasting blood glucose is monitored. Oral glucocorticoids are typically administered so that they mimic the physiological pattern of endogenous cortisol secretion, and once-daily glucocorticoids such as prednisone and prednisolone are administered in the morning. Taking into account the peak effect of these medications after a dose (e.g. peak effect of prednisone at 4–6 hours), checking a 1–2 hours post-lunch or a pre-dinner blood glucose starting a few days after treatment initiation will enable detection of any hyperglycaemia [11, 18, 19]. An elevation in the fasting blood glucose can occur with higher doses of once-daily glucocorticoids (prednisone 40 mg or equivalent) and with twice-daily administration [19]. People with pre-existing diabetes should monitor their blood glucose more frequently during the course of glucocorticoid treatment and all treated individuals should also be advised to look out for symptoms of hyperglycaemia. There are no published guidelines on the treatment of glucocorticoid-induced hyperglycaemia with diabetes medications, although various strategies have been advocated [11, 19].

Oral agents that enhance insulin sensitivity (e.g. metformin, thiazolidinediones) or stimulate insulin secretion (e.g. sulfonylureas, non-sulfonylurea secretagogues) address the mechanisms underlying glucocorticoid-induced hyperglycaemia. However, concerns about pre-existing renal impairment and other risk factors for lactic acidosis, long duration of action leading to hypoglycaemia especially overnight, or slow onset of effect plus weight gain and oedema make the use of metformin, sulfonylureas, and thiazolidinediones, respectively, not an ideal option in some individuals [11, 19]. The non-sulfonylurea secretagogues and dipeptidyl peptidase-4 inhibitors may be better choices given their quicker onset of action, effect on post-prandial hyperglycaemia, and lower potential for hypoglycaemia [18]. Insulin therapy offers the flexibility of matching the onset, peak, and duration of action to the pattern and degree of hyperglycaemia; furthermore, the dose can be more easily adjusted when the glucocorticoid dose is changed. Neutral protamine Hagedorn (NPH) insulin or a premixed insulin containing NPH can be the best choice for people with diabetes taking an intermediate-acting glucocorticoid (e.g. prednisone) in the morning [11, 18, 19]. When given once daily at breakfast, NPH insulin's peak effect starting at 4 hours after administration and duration of 10–16 hours closely matches the peak effect and duration of prednisone. In individuals taking a long-acting glucocorticoid, such as dexamethasone, twice-daily dosing of intermediate-acting glucocorticoids, and higher doses (e.g. 40 mg or higher of prednisone or equivalent), fasting hyperglycaemia will likely also be seen and a long-acting insulin analogue (glargine, detemir, or degludec) plus prandial insulin will likely be needed [18, 19]. Many courses of treatment with glucocorticoids comprise an initial high dose with a gradual taper to physiological levels before eventual discontinuation. Careful monitoring of blood glucose and subsequent insulin dose adjustments may be necessary to avoid hypoglycaemia as the medication is withdrawn. The results of an ongoing Danish multicentre randomized control trial comparing NPH insulin with the sodium-glucose cotransporter-2 (SGLT-2) inhibitor empagliflozin (EANITIATE study) for individuals with glucocorticoid-induced diabetes may provide additional insight into management strategies [20].

Second-generation antipsychotics

The SGAs, also known as atypical antipsychotics, constitute another drug class with well-known hyperglycaemic effects (Chapter 65). Numerous case reports as well as studies exist of various SGAs worsening existing diabetes, inducing new-onset diabetes, and leading to hyperglycaemic crises [21–24]. SGAs can cause blood glucose elevations both acutely and chronically [25–27]. Hyperglycaemia has been reported for all currently marketed SGAs in the USA, although the degree of severity varies considerably [26, 28–30]. Olanzapine and clozapine appear to have the highest propensity for this adverse drug reaction [26, 27, 31]. SGAs with the lowest potential for hyperglycaemia include the newer SGAs, aripiprazole, ziprasidone, paliperidone, lurasidone, brexiprazole, and cariprazine, although data and clinical experience with these agents are more limited [28–30, 32, 33]. Quetiapine and risperidone have moderate potential for hyperglycaemia relative to the other SGAs [29].

The mechanism of SGA-induced hyperglycaemia has yet to be fully elucidated, but is likely multifactorial. SGA-induced weight gain is probably an important contributor, and SGAs with the highest potential for weight gain (olanzapine and clozapine) are also associated with the most clinically significant hyperglycaemia. The binding of SGAs to histamine-1, serotonin, norepinephrine, and dopamine receptors, at different affinities depending on the agent, affects weight gain through regulation of hunger and satiety [29]. However, several studies also demonstrated that hyperglycaemia and insulin resistance occur with some SGAs regardless of body weight and food intake [34, 35]. Animal studies suggest that SGAs may induce hyperglycaemia through inhibition of insulin secretion by antagonism of α-1 adrenergic, muscarinic (M_3), and serotonergic ($5HT_2$) receptors [36, 37].

Similar to glucocorticoids, SGA administration can lead not only to hyperglycaemia, but also to weight gain and dyslipidaemia, which further contribute to cardiovascular risks. These adverse drug reactions, along with the higher prevalence among individuals with mental illness of overweight or obesity, physically inactivity, and smoking, make monitoring and prompt treatment crucial [38]. A large meta-analysis encompassing 25 692 people with schizophrenia found an overall prevalence of 32% for metabolic syndrome, and 52%, 28%, 28%, and 20% for clozapine, olanzapine, risperidone, and unmedicated individuals, respectively [39].

Recommendations for monitoring for the development of hyperglycaemia, weight gain, and dyslipidaemia were first published in 2004 by the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity [29], but other national and international guidelines have also emphasized the importance of regular screening for glucose and lipid abnormalities [40, 41]. In addition to obtaining personal and family history of diabetes, dyslipidaemia, hypertension, obesity, and cardiovascular disease, these guidelines also recommend obtaining baseline measurement for glucose, lipids, blood pressure, and body mass index with periodic reassessment. A proposed monitoring schedule can be found in Table 21.2 [42]. Specific to fasting plasma glucose, this should be monitored at 12 weeks then annually. In addition, if the person gains ≥5% of their baseline weight during treatment, it is recommended that clinicians consider switching to another SGA [29]. Several studies have shown an improvement in glucose levels after switching from olanzapine to aripiprazole [43].

Table 21.2 Monitoring schedule for second-generation antipsychotics.

Measurement	Baseline	6 weeks	12 weeks	At least annually
Weight and body mass index	X	Measure weekly in first 6 weeks	X	X
Waist circumference	X	X	X	X
Fasting glucose	X	X	X	X
Fasting lipid profile	X	X	X	X
Blood pressure	X	X	X	X

Source: American Diabetes Association et al. 2004 [29].

However, changing to another antipsychotic may not always result in equivalent treatment of the mental illness and other measures (therapeutic lifestyle changes, diabetes medications) may need to be employed.

Oral contraceptive agents

Combination oral contraceptive (COC) preparations are used by more than 100 million women worldwide [44]. These products contain one of two oestrogens, mestranol or ethinyl oestradiol, and a variety of progestins (e.g. norethindrone, norgestrel, norgestimate) in monophasic, biphasic, and triphasic formulations. Despite their proven efficacy, adverse events have been ascribed to their use (especially the oestrogen component), including metabolic abnormalities such as glucose intolerance and overt diabetes. The causes of COC-induced dysglycaemia have been historically associated with alterations in insulin sensitivity and insulin secretion. However, current evidence does not support a significant effect of COCs on glucose metabolism or homeostasis and the development of overt diabetes [45]. Interestingly, a recent analysis of data from the Missouri Pregnancy Risk Assessment Monitoring System (PRAMS) in the USA suggested that women with gestational diabetes were nearly 1.5 times more likely to have used hormonal contraception before conception [46]. A recently published Cochrane Database systematic review sought to answer the question of whether COCs adversely affected carbohydrate metabolism in women without diabetes and in those with overweight or obesity. In analysing 31 trials that met the inclusion criteria, there were no significant differences in carbohydrate metabolism among the different preparations. Surrogate end-points used included fasting and two-hour post-prandial glucose, insulin and glucose area-under-the curve (AUC), and glycated haemoglobin (HbA_{1c}) levels. Due to various study design deficiencies, the authors were unable to elucidate the metabolic risk of oral contraceptives in women with obesity [47].

Whereas the risk of dysglycaemia from COCs in women without diabetes remains negligible, metabolic effects arising from the use of these drugs in women with type 1 diabetes or type 2 diabetes can be consequential. Similarly, unplanned pregnancy in this same population also has significant maternal and fetal consequences, especially when associated with hyperglycaemia. Thus contraceptive options must be chosen that do not contribute to an excess metabolic and cardiovascular risk for these women. Based on the eligibility criteria

for contraceptive use published by the World Health Organization (WHO) in 2009 (adapted by the USA in 2010), the use of COCs is favoured in women with type 1 diabetes or type 2 diabetes without vascular complications and in women with a history of gestational diabetes [45]. A 2013 Cochrane Database systematic review failed to show significant differences between progestin-only, combination hormonal, and non-hormonal contraceptives on carbohydrate and lipid metabolism and vascular complications in women with type 1 diabetes or type 2 diabetes [48]. These results were ascribed to various methodological deficiencies, making interpretation problematic.

Menopause hormone therapy

Menopause hormone therapy (MHT) or hormone replacement therapy (HRT) typically involves the administration of oral oestrogens alone or in combination with an oral progestogen for the treatment of postmenopausal symptoms, especially hot flashes, vaginal atrophy, and mood instability. Transdermal and intravaginal formulations are also prescribed. Given the potential for COCs to affect glucose homeostasis and glycaemic indices in women with diabetes, the use of MHT in postmenopausal women can be viewed with similar concerns, especially with oral preparations, as the doses are typically higher than with other routes of administration [49]. The results of two published randomized placebo-controlled trials have dispelled the concern about whether MHT adversely impacts glucose metabolism or precipitates incident diabetes. The Heart and Estrogen/Progestin Replacement Therapy Study (HERS) studied nearly 2800 postmenopausal women with coronary heart disease who took MHT for approximately four years [50]. At the completion of the trial, there was no significant difference in the fasting blood glucose levels between women with and without diabetes and those with impaired fasting glucose. Importantly, women taking MHT had a 35% reduction in incident diabetes compared to those in the placebo arm of the trial (number needed to treat [NNT] = 30 over 4 years). Likewise, women enrolled in the Women's Health Initiative Hormone Trial and receiving conjugated equine oestrogens plus medroxyprogesterone were found to have a 21% lower risk of diabetes ($p = 0.03$) at one-year follow-up compared to placebo controls (NNT = 143 over 5.6 years) [51]. This difference was ascribed to decreases in insulin resistance. Reduced incident diabetes was also noted in a recent meta-analysis of postmenopausal women on low-dose combination HRT [52]. In the same study women with diabetes experienced improved metabolic measures. The findings suggest that postmenopausal women can safely take MHT without adversely affecting glucose homeostasis or triggering diabetes.

Whether women with diabetes can safely take MHT remains more uncertain and untested. A recently published Cochrane Database systematic review showed that glycaemic levels were not affected by MHT in women with type 1 diabetes [53]. However, this finding was based on only one underpowered placebo-controlled randomized clinical trial, making the results questionable. Previous studies evaluating the effects of MHT on women with type 2 diabetes suggest improved glycaemic levels with its use [54, 55]. In a large observational study, investigators evaluated the impact of MHT (opposed and unopposed oestrogen therapy) on HbA_{1c} in women with type 2 diabetes. HbA_{1c} was significantly lower in women taking MHT versus those not on MHT: age-adjusted mean ± standard error [SE] 7.9 ± 0.03% (63 mmol/mol) vs 8.5 ± 0.02% (69 mmol/mol), respectively, $p = 0.0001$ [55]. Likewise, an assessment of data from the US National Health and Nutrition Examination Survey, 1988–1994 (NHANES III). indicated that postmenopausal women currently taking MHT had lower fasting blood glucose and HbA_{1c} levels versus women who had never taken MHT: 112 vs 154 mg/dl (6.2 mmol/l vs 8.5 mmol/l) and 6.0% vs 7.1%, (42 mmol/mol vs 54 mmol/mol), respectively. Whereas these observational studies cannot support causation, the evidence does promote the notion that MHT has minimal impact on established type 2 diabetes in postmenopausal women. Continued surveillance of glycaemic indices is prudent in these women and appropriate adjustments should be made to their anti-diabetes drug regimens as needed.

Thiazide diuretics

The thiazide diuretics have been a mainstay for the management of hypertension for over 50 years [56]. Early on it was recognized that this drug class could negatively impact glycaemic measures in persons with diabetes [57]. Despite their widespread use and clinical utility, questions continue to be raised regarding their potential effect on glucose homeostasis and glycaemic levels in those with established diabetes. In a recent systematic review and meta-analysis, thiazide diuretics exhibited a dose-dependent modest effect on fasting blood glucose and a negligible effect on HbA_{1c} in people with hypertension [58]. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a very large landmark study in hypertension management, found significantly more new-onset diabetes (fasting blood glucose ≥126 mg/dl [7 mmol/l]) with chlortalidone compared to amlodipine and lisinopril at the four-year follow-up period (11.6%, 9.8%, and 8.1%, respectively) [59]. In addition, people with pre-existing diabetes or those who developed diabetes during the original Systolic Hypertension in the Elderly Program (SHEP) were evaluated as part of a long term follow-up study (14.3 years) [60]. Individuals with diabetes assigned to chlortalidone had lower cardiovascular and total mortality rates compared to placebo controls (hazard ratio [HR] 0.805, 95% confidence interval [CI] 0.680 to 0.952) [60]. These representative studies, although interesting in their findings, provide little resolution to the ongoing debate surrounding thiazide-induced dysglycaemia.

Historically, thiazide-induced dysglycaemia has been connected to alterations in potassium balance, namely hypokalaemia. Since insulin secretion is linked, in part, to an accumulation of intracellular potassium within the pancreatic β cell, potassium loss would impair insulin release, resulting in hyperglycaemia. In an effort to substantiate this long-held belief, a group of investigators reviewed pertinent intervention trials using thiazides from 1966 to 2004 that measured serum potassium and glucose levels [61]. There were 59 trials that met the inclusion criteria. Analysis of the trial data supported an inverse relationship between potassium balance and blood glucose levels. However, the effects on blood glucose were modest, with an average increase of 7.07 ± 7.38 mg/dl (0.4 ± 0.4 mmol/l) [61]. In a subgroup analysis of the SHEP trial, for every 0.5 mEq/l (0.5 mmol/l) decrease in serum potassium there was a corresponding 45% increase in incident diabetes risk (95% CI 24% to 70%; $p < 0.001$) [62]. This association was only evident during the first year of treatment with chlortalidone. In a more recent subgroup analysis, no correlation was found between fasting serum glucose and serum potassium levels in individuals with hypertension receiving hydrochlorothiazide alone or when added to atenolol [63].

Clinicians need to be aware that the thiazide diuretics can affect glucose homeostasis in a dose-dependent manner, but the effect appears to be modest at best. Maintaining normokalaemia is the best defence against this potential metabolic consequence of thiazide use [62]. Any alteration in glycaemic levels can be managed with careful adjustment of the anti-diabetes regimen and continued blood glucose monitoring.

β-adrenoceptor antagonists

β-blockers are widely used to treat a variety of conditions, including hypertension, angina, arrhythmias, and congestive heart failure. Despite their benefits, these drugs can pose problems for people with pre-existing diabetes. Their propensity to mask the adrenergically mediated signs and symptoms of hypoglycaemia and delay its recovery is well known. Theoretically, non-selective β-blockers could also worsen peripheral vascular disease via unopposed α-receptor stimulation of the vasculature. Whether β-blockers affect glucose homeostasis or contribute to the development of overt diabetes is less certain. In a recent meta-analysis and systematic review, non-selective β-blockers were associated with an increase in fasting blood glucose of ~10 mg/dl (0.5 mmol/l) in persons with diabetes. Importantly, adverse outcomes were not noted [64].

In an older prospective cohort study, the use of β-blockers was associated with a 28% increased risk of new-onset diabetes (relative hazard 1.28; 95% CI 1.04 to 1.57) [65]. A more recent systematic literature review examined the effects of various β-blockers on glucose homeostasis, insulin sensitivity, and diabetes risk [66]. β-blockers with vasodilating properties had less pronounced effects on glycaemic indices and insulin sensitivity in people with diabetes. Whereas the evidence supporting an association between the administration of selective and non-selective β-blockers and diabetes risk is inconclusive, β-blockers with α-blocking properties (e.g. carvedilol) may have a reduced or no risk for diabetes [67]. This discrepancy has been attributed to differences in effects on insulin sensitivity compared to conventional β-blockers. These findings warrant consideration of a β-blocker with vasodilating properties, such as carvedilol and nebivolol, as the preferred choice for people with diabetes or those at high risk for diabetes [66].

HMG CoA reductase inhibitors

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, commonly known as statins, have been the mainstay of hyperlipidaemia and cardiovascular protection for over two decades, but their hyperglycaemic potential has only recently been reported. The US Food and Drug Administration (FDA) changed the product labelling of statin medications to include the findings of elevated fasting glucose and HbA_{1c} in 2012 [68]. Statins appear to increase insulin resistance and decrease insulin secretion, with small increases in HbA_{1c} and fasting glucose [69]. A meta-analysis reported that the lowest risk for new-onset diabetes is with pravastatin at 40 mg/day (odds ratio [OR] 1.07, 95% CI 0.86 to 1.3), followed by atorvastatin 80 mg/day (OR 1.15, 95% CI 0.9 to 1.5), and highest with rosuvastatin 20 mg/day (OR 1.25, 95% CI 0.82 to 1.9) when compared to placebo [70]. Another meta-analysis found that the risk of incident diabetes is 9% (OR 1.09, 95% CI 1.02 to 1.17) and that treatment of 255 individuals for four years would result in one additional case of diabetes [71]. The authors also reported that statin therapy would prevent 5.4 major coronary events (coronary heart disease death and non-fatal myocardial infarction) in these 255 individuals, and that the potential benefit would be expected to be greater if prevention of strokes and revascularization was also taken into account [71]. The Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial reported that, for those with one or more diabetes risk factors, rosuvastatin was associated with a 28% increase in diabetes, but 134 cardiovascular events or deaths were avoided for every 54 new cases of diabetes [72]. The American Diabetes Association Standards of Medical Care in Diabetes guideline noted that the absolute risk of rosuvastatin-induced diabetes is small (1.5% with rosuvastatin compared to 1.2% with placebo over five years) and recommends statin therapy for most people with diabetes with overt cardiovascular disease or cardiovascular risk factors [73,74].

Antiretroviral therapy for human immunodeficiency virus

The pharmacological treatment of human immunodeficiency virus (HIV)-1 currently includes nucleoside reverse-transcriptase inhibitors (NRTIs), non-nucleoside reverse-transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors, fusion inhibitors, chemokine receptor antagonists, CD4 post-attachment inhibitors, and gp120 attachment inhibitors. Hyperglycaemia and diabetes have been reported with PIs and some of the NRTIs (zidovudine, stavudine, and didanosine) [75]. In a recent meta-analysis, the incidence of diabetes and pre-diabetes in people taking antiretrovirals was 13.7 and 125 per 1000 person-years. Risk factors included age, obesity, family history, lipodystrophy, and antiretroviral therapy regimen [76]. NRTIs can cause insulin resistance and promote lipodystrophy and pancreatitis [1,77,78]. PIs induce hyperglycaemia through increasing insulin resistance and the development of lipodystrophy [79–85]. *In vitro* studies also demonstrated that some PIs can decrease insulin secretion [81,85]. PI-induced lipodystrophy (Figure 21.1) is characterized by lipohypertrophy (resembling central obesity) with or without lipoatrophy, manifesting as peripheral fat loss (particularly in the extremities, face, and buttocks) [86]. Lipodystrophy, insulin resistance, hyperglycaemia, and the dyslipidaemia (elevated triglyceride and total cholesterol, reduced high-density lipoprotein cholesterol) associated with PIs can increase the risk of cardiovascular events in treated individuals. In 2021, HIV diagnosis was incorporated into the American Diabetes Association's Standards of Medical Care in Diabetes guideline as a risk factor that warrants screening. The guideline specifically recommended that 'Individuals with HIV should be screened for diabetes and prediabetes with a fasting glucose test before starting antiretroviral therapy, at the time of switching antiretroviral therapy, and three to six months after starting or switching antiretroviral therapy. If initial screening results are normal, fasting glucose should be checked annually' [87].

Pentamidine

Pentamidine is an antifungal/antiprotozoal agent, which is FDA-approved for the treatment and prevention of *Pneumocystis jirovecii* pneumonia commonly associated with HIV infection and those

Figure 21.1 Protease inhibitor-induced lipodystrophy. (a, b) 'Buffalo hump' caused by nuchal fat deposition. (c, d) Facial fat atrophy. Source: Courtesy of Professor Munir Pirmohamed, University of Liverpool, UK.

with immunodeficiency or malignancy. The drug is usually administered intravenously or via inhalation for adults and children alike. Importantly, the drug has the propensity to cause both hypoglycaemia and hyperglycaemia. Its well-known dysglycaemic effects are due to impaired insulin secretion and direct cytotoxicity and β-cell apoptosis. In 128 immunocompromised individuals with *P. jirovecii* pneumonia, pentamidine was associated with 7 cases of hypoglycaemia, 23 cases of overt diabetes, and 18 cases of hypoglycaemia followed by diabetes. The drug was administered parenterally in 75% of the individuals. Hyperglycaemia was noted an average of 52 days (20–90 days) following pentamidine administration. Insulin was required in 63% of those with diabetes. Risk factors for the development of diabetes included high doses, impaired renal function, and poor clinical status of the individual [88]. In a retrospective chart review of pentamidine-associated adverse drug reactions in 106 HIV-infected people, 9 experienced hyperglycaemia, with average blood glucose levels of 369 mg/dl (20.4 mmol/l) and a mean time to onset of 14 days [89]. Providers need to be aware of the development of hyperglycaemia with pentamidine and monitor the individual accordingly for this late-appearing adverse drug reaction.

Fluoroquinolones

The fluoroquinolone class of antimicrobial agents has been available for over 50 years. Despite these drugs' clinical utility, several well-known adverse effects have been reported, most noteworthy being arthropathy and QT prolongation [90]. In retrospective analyses, serious dysglycaemia (both hypoglycaemia and hyperglycaemia) has also been associated with their use, culminating in the voluntary removal of gatifloxacin from the US and Canadian markets in 2006 owing to a significant risk of hospitalization for hypoglycaemic or hyperglycaemic episodes [91, 92]. Although oral gatifloxacin is no longer available from many markets (e.g. USA, Canada, Japan, India), it is still sold around the world and is

available via online distributors. In 2018, the FDA announced additional warnings for the fluoroquinolone class to include the potential for hypoglycaemic coma, especially in older people and those taking oral anti-diabetes agents and/or insulin [93]. Inhibition of adenosine triphosphate (ATP)-dependent potassium channels on pancreatic β cells resulting in increased insulin secretion may play an aetiological role [94].

Whereas many drug adverse effects are a class effect, fluoroquinolone-associated dysglycaemia appears to be much more common with gatifloxacin compared to levofloxacin. Ciprofloxacin poses little or no risk [92]. Of the currently available fluoroquinolones in the USA, moxifloxacin appears to have the highest likelihood for causing hyperglycaemia compared to levofloxacin or ciprofloxacin. A recent large population-based cohort study of approximately 78 000 individuals in Taiwan found that the overall risk of hyperglycaemia and hypoglycaemia was greater with moxifloxacin compared to levofloxacin, ciprofloxacin, macrolides, and second-generation cephalosporins [95].

The aetiology of fluoroquinolone-induced hyperglycaemia is unclear, but possible contributing factors include a history of diabetes, failure to adjust doses in renal insufficiency, acute illness, and age. Recent animal studies suggest that hyperglycaemia results from increased drug accumulation in the pancreas of individuals with diabetes, histamine-associated release of the counter-regulatory hormone epinephrine, and the prolonged secretion of glucagon-like peptide 1 (GLP-1), which inhibits insulin secretion and production [96–98].

The risk of hyperglycaemia from fluoroquinolone use (with and without diabetes) warrants careful surveillance by clinicians and those taking the drugs alike. Hyperglycaemia tends to occur within 1–2 weeks of therapy initiation and is dose related. Any changes in glycaemic indices can be managed with careful adjustment of the anti-diabetes regimen and continued blood glucose monitoring. Likewise, hypoglycaemic signs and symptoms must be verified and managed accordingly. Adjustments of oral anti-diabetes and insulin therapy may be required. Recent evidence supports a possible role for octreotide in the management of refractory fluoroquinolone-induced hypoglycaemia [94].

Calcineurin inhibitors

There are various classes of drug that are used as immunomodulators to combat rejection following organ transplantation or to manage autoimmune diseases and other inflammatory conditions. One such class is the calcineurin inhibitors. Well-known representative examples include cyclosporine and tacrolimus. Calcineurin is a protein that is involved in the production of the cytokine interleukin-2 (IL-2) by T-helper cells. IL-2 is responsible for T-cell differentiation, which is important in the maintenance of cellular immunity.

It had been recognized for many years that transplant recipients experience glucose intolerance and also develop type 2 diabetes [99]. Several associated risk factors were implicated in the development of post-transplant hyperglycaemia or diabetes, including the widespread use of corticosteroids in this population. In addition to the transplant itself, immunosuppressant agents administered to counteract rejection were also implicated, namely cyclosporine and tacrolimus [99]. The prevailing belief that cyclosporine is less likely to impair glucose homeostasis than tacrolimus has been questioned [100]. Alterations in insulin sensitivity and impaired β-cell function are cited as causative factors in the development of glucose intolerance. However, recent evidence corroborates findings that defective insulin secretion is the primary pathological defect [101]. Whether cyclosporine has any advantages over tacrolimus in managing transplant recipients with pre-existing type 2 diabetes has recently come into question, yet remains controversial [102, 103].

Risk factors for new-onset diabetes after transplantation (NODAT) include older age, obesity, corticosteroid use, other-than-White ethnicity, hepatitis C, and genetic determinants [104]. Glucose intolerance or overt diabetes tends to occur within six months of immunosuppressant therapy. Clinicians need to be aware of individual risk factors and aggressively manage dysglycaemia when it occurs. Inattention to NODAT can result in graft failure and other diabetes-related complications [104]. The optimal therapeutic approach remains to be defined, but emerging evidence suggests that insulin secretagogues, the dipeptidyl peptidase 4 (DPP-4) inhibitors, and basal insulin may be suitable drug options [104–106].

Diazoxide

Diazoxide is a thiazide-like drug that had been in clinical use for over 40 years for the management of hypertensive emergencies and hyperinsulinaemic hypoglycaemia (secondary hypoglycaemia). At present, the drug is only available as an oral suspension for the treatment of secondary hypoglycaemia (e.g. insulinoma, islet cell hyperplasias). Importantly, it has been long recognized as a cause of drug-induced hyperglycaemia and even diabetic ketoacidosis [107]. Its hyperglycaemic effects have been purported to result from impaired insulin secretion, increased glucose production, and decreased peripheral glucose utilization [108, 109]. Diazoxide's ability to inhibit insulin secretion results from *opening* the ATP-sensitive potassium (K_{ATP}) channel in the β cell of the pancreas. This ability to inhibit insulin secretion may prove useful in the management of type 1 diabetes and type 2 diabetes by preserving β-cell function [110]. Likewise, diazoxide may improve hypoglycaemic unawareness via opening the sulfonylurea receptor 1 (SUR1)-selective K_{ATP} channels in the central nervous system [110].

Prevention and treatment strategies

The old adage that an ounce of prevention is worth a pound of cure is germane to any discussion involving drug-induced dysglycaemia. Clinicians need to be sensitized to the reality that drug therapy may precipitate hyperglycaemia in predisposed individuals as well as lead to overt diabetes mellitus. It may be best to avoid precipitant drugs whenever possible and choose more appropriate alternatives. When evaluating a possible case of drug-induced dysglycaemia, a careful review of prescription and non-prescription (over-the-counter) medications as well as herbal products and dietary supplements can reveal possible offenders. In addition to a thorough drug history, the clinician should also evaluate the individual person's drug regimen and comorbid conditions that may affect the pharmacokinetics or pharmacodynamics of the suspected drug. When drug–drug interactions are suspected, numerous resources are available to the clinician to facilitate their evaluation. These include various compendia, online references, smartphone applications,

professional colleagues, and drug and health information centres. As with any reference tool, it is important to corroborate the information found using a second or third source. This ensures that the information is timely, accurate, and reliable.

Clinicians are often stymied when assessing non-prescription medications by the sheer number of products available for consumption. One can overcome this fact by employing a review of systems approach, akin to asking the individual about organ system-based complaints as part of a medical history. In this systematic approach, major product categories are captured and evaluated by asking *head-to-toe* questions. This method has been previously published if more information is needed [111].

Whenever possible, limit an individual's exposure to drugs that could affect glucose regulation. Careful attention should be paid to limiting the numbers of drugs, as well as the doses and duration of therapy whenever possible. Baseline data such as weight, renal function, and fasting blood glucose levels should be obtained when appropriate. This is especially important in individuals taking more than one medication with the potential for hyperglycaemia, prescribed a high dose of the medication, taking concomitant drugs that can increase the concentration or duration of the medication, or those with other risk factors for diabetes (Table 21.3) [1,74]. Importantly, prospective monitoring of high-risk individuals should be an ongoing process.

In the event that a precipitant drug cannot be avoided in a given person, prudence would dictate careful monitoring for the occurrence of dysglycaemia. If a morbid event occurs, the dose of the offending agent can be reduced or the drug can be discontinued if suitable. If necessary, supportive care may be required for a time dependent on the drug in question and the clinical status of the individual. Most importantly, the clinician should learn from the incident and develop strategies to obviate such happenings in the future.

Table 21.3 Risk factors for diabetes.

Age ≥35 years
Family history (first-degree relative) of diabetes
Race/ethnicity (e.g. African American, Latino, Indigenous American, Asian American, Pacific Islander)
Physical inactivity
Overweight or obese (body mass index ≥25 kg/m^2 or ≥23 kg/m^2 in Asians)
Hypertension (≥140/90 mmHg in adults or on therapy for hypertension)
High-density lipoprotein cholesterol <35 mg/dl (0.90 mmol/l) and/or triglyceride level >250 mg/dl (2.82 mmol/l)
History of cardiovascular disease
History of gestational diabetes
HIV
Polycystic ovary syndrome
Previously identified pre-diabetes based on laboratory values
Other clinical conditions associated with insulin resistance (e.g. acanthosis nigricans, severe obesity)

Source: ElSayed et al. 2023 [87].

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22 Diabetes in Hypersecreting Endocrine Disorders

Allan A. Vaag[1], Neil A. Hanley[2], and Caroline M. Kistorp[1]

[1] Steno Diabetes Center Copenhagen and Rigshospitalet, Copenhagen, Denmark

[2] Centre for Endocrinology and Diabetes, University of Manchester, Manchester, UK

Key points

- Hypersecretion of glucocorticoids in Cushing syndrome is associated with insulin resistance and impaired glucose homeostasis in around 70% of cases.
- Hypersecretion of growth hormone from adenomas in the anterior pituitary causes acromegaly, which is associated with impaired glucose homeostasis in up to 38% of all individuals with the disease.
- Hypersecretion of catecholamines from adenomas of the chromaffin cells in the adrenal medulla or paraganglioma causes hyperglycaemia in approximately 50% of cases.
- Hypersecretion of glucagon or somatostatin from pancreatic islet cell adenomas is a rare endocrine cause of diabetes.
- Hypersecretion of thyroid hormones in thyrotoxicosis causes mild and most often transient glucose intolerance.
- Hypersecretion of aldosterone, parathyroid hormone, or vasoactive intestinal peptide due to hyperplasia or adenoma is associated with mild glucose intolerance.
- Hypersecretion of androgenic steroids causes insulin resistance and glucose intolerance in up to 50% of women with polycystic ovarian syndrome.

Diabetes is defined by arbitrary cut-off levels of plasma glucose and/or glycated haemoglobin (HbA_{1c}) levels, thought to reflect the level of glycaemia that differentiates between people with or without risk of micro- and macrovascular diabetes complications. However, with insufficient knowledge of the exact causal or non-causal relationships between glycaemia and each of the multiple distinct vascular and non-vascular complications, and without being able to exactly factor in the time and duration of the diabetes dimension, it is clear that there is a grey zone in which people may be misclassified as either having or not having diabetes. Obviously, this dimension is of higher importance in type 2 diabetes compared with type 1 diabetes. Furthermore, this issue has increasing importance in those with relatively mild diabetes secondary to the general activation of stress responses in individuals with a range of different diseases, including infections, acute severe illness, cancer, and heart failure. Multiple types of cancer as well as heart failure often precede and even may be the primary cause of diabetes in some individuals [1]. An intriguing dimension of this is that the excess morbidity and mortality in people with diabetes secondary to other diseases may not necessarily be due to diabetes *per se* [1], and that the otherwise unexplained U-shaped relationship between HbA_{1c} and mortality in type 2 diabetes could reflect different causes of death in individuals with high versus low HbA_{1c}, with the latter population more likely to die from other diseases than diabetes [1]. The mechanism by which multiple types of endocrine disorders and diseases cause diabetes reflects activation of stress hormones, including growth hormone (GH), catecholamines, steroids, glucagon, and thyroid hormones. In that context, it is not difficult to understand why pathological overproduction and hypersecretion of these hormones may cause or precipitate overt diabetes, which for most cases phenotypically resembles type 2 diabetes, but probably more correctly should be classified as secondary diabetes. The aim of this chapter is to provide a brief overview of endocrine disorders that cause secondary and often transient diabetes as a result of uncontrolled excessive secretion of *counter-regulatory hormones* involved in physiological regulation of glucose homeostasis and protection against hypoglycaemia on a daily basis.

Acromegaly

Clinical presentation

Acromegaly is caused by excessive GH secretion leading to bone and soft tissue overgrowth as well as cardiovascular and metabolic complications (Figure 22.1, Table 22.1) [2]. Acromegaly affects between 60 and 240 people per million [2] and is most frequently caused by a pituitary adenoma larger than 1 cm in diameter (a *macroadenoma*; Figure 22.1). Acromegaly may less frequently be caused by a *microadenoma* (diameter less than 1 cm) and a minority (<1%) of cases are caused by excessive secretion of GH-releasing hormone (GHRH) from a hypothalamic gangliocytoma or a carcinoid tumour in the pancreas or the lung [3]. Acromegaly may in rare cases appear as part of the multiple endocrine neoplasia type 1 and type 4 (MEN1) syndrome as a result of a mutation in the tumour suppressor gene, *MENIN* [4]. MEN1 can also include

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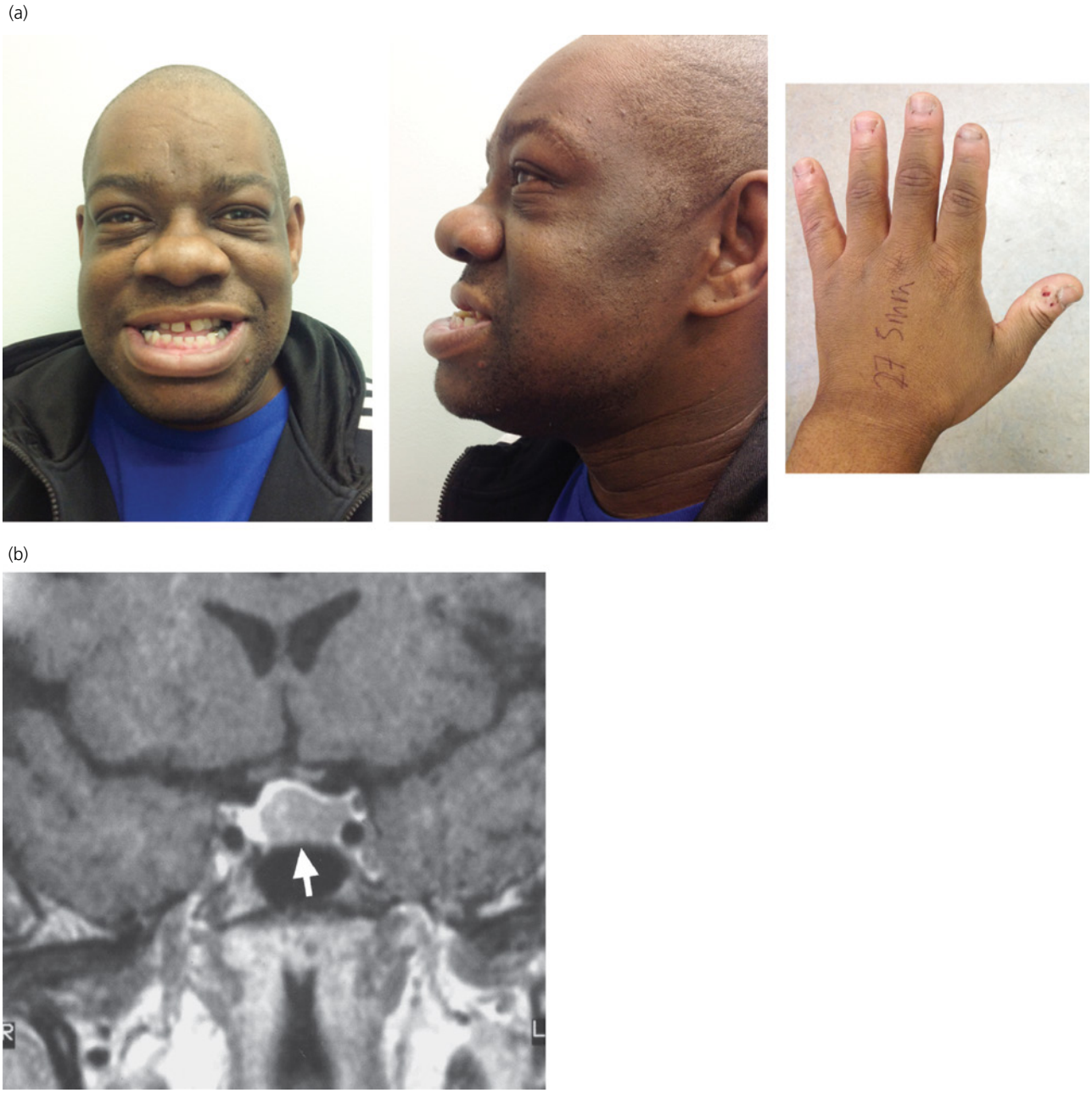


Figure 22.1 (a) Characteristic features of a man with untreated acromegaly. Note the teeth separation, particularly noticeable in the lower jaw, and the associated underbite from the mandibular overgrowth. The hand illustrates soft tissue overgrowth and is often described as spade-like. (b) Magnetic resonance imaging from an individual shows a large adenoma (arrow) in the pituitary extending up to but not in contact with the optic chiasm and also extending out into the left cavernous sinus. Source: Courtesy of Professor Neil Hanley and Rachel Jennings, University of Manchester, UK.

glucagonomas and somatostatinomas, both of which can independently cause secondary diabetes. Acromegaly may in rare cases occur in familial isolated pituitary adenomas as a result of mutations in the aryl hydrocarbon receptor-interacting protein (*AIP*) tumour suppressor gene, which is associated with early onset and a more aggressive disease [5]. Acromegaly has most often been present several years prior to the clinical diagnosis based on the characteristics outlined in Figure 22.1 and Table 22.1 [1]. Onset of acromegaly in adolescence prior to the closure of linear growth results in excessive adult height or *gigantism*. Untreated GH excess is associated with hypertension, increased morbidity, and mortality from cardiovascular disease as well as glucose intolerance [1].

Glucose intolerance

Abnormal glucose tolerance or overt diabetes occurs in 15–38% of all individuals with acromegaly as a direct result of elevated GH and insulin-like growth factor I (IGF-I) levels (Figure 22.2) [6]. Indeed, the severity of diabetes and to some extent insulin resistance correlates directly with the degree of elevated GH and IGF-I levels in acromegaly [7].

Table 22.1 Clinical features of acromegaly.

Musculoskeletal
Protruding mandible (prognathia) with lower teeth separation
Big tongue (macroglossia)
Enlarged forehead (frontal bossing)
Acral growth of hands and feet (carpal tunnel syndrome, tight rings, increasing shoe size)
Large joint arthropathy and arthralgia
Gigantism (if growth hormone excess prior to epiphyseal closure)

Skin
Irritating, thickened, greasy (increased sebum production)
Excessive sweating

Cardiovascular
Dilated cardiomyopathy, cardiomegaly, and cardiac failure
Hypertension

Metabolic
Glucose intolerance/diabetes

General
Headaches
Tiredness, often very disabling, lowers quality of life and ability to work

Local tumour effects
Compression of the optic chiasm (superior tumour growth) or cranial nerves III, IV, and/or VI (lateral tumour growth into cavernous sinus)

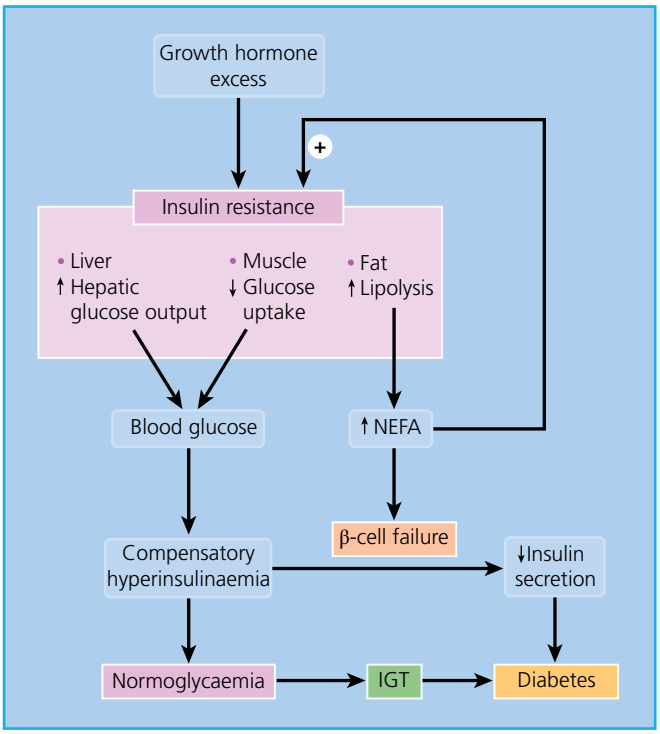


Figure 22.2 Mechanisms of hyperglycaemia and diabetes in acromegaly. Diabetes develops if β cells fail to compensate for the increased demand for insulin. IGT, impaired glucose tolerance; NEFA, non-esterified fatty acid.

Diabetes in acromegaly resembles mild or moderately severe type 2 diabetes. Insulin treatment is rarely required, and most individuals can be treated with diet and oral anti-diabetes drugs [6]. The underlying pathogenic mechanisms of diabetes in acromegaly resemble common type 2 diabetes, including both hepatic and peripheral (muscle) insulin resistance, as well as impaired pancreatic insulin secretion in either a relative or an absolute sense [8]. GH is a strong enhancer of adipose tissue lipolysis generating non-esterified fatty acids (NEFAs), which in turn via the *glucose–fatty acid* cycle (Figure 22.2) cause both hepatic and muscle insulin resistance, as well as with time also impaired pancreatic insulin secretion, eventually resulting in overt hyperglycaemia [8].

Diagnosis and treatment

The simplest and most frequently used screening test for acromegaly is a measurement of the serum IGF-I level [3]. If markedly raised above the reference, and exogenous GH administration is excluded, the test is diagnostic for acromegaly, but is primarily used as a rule-out measure [3]. Subsequent diagnostic tests include a series of random serum GH measurements, and/or a two-hour 75 g oral glucose tolerance test (OGTT), with the latter taking advantage of the negative feedback by glucose on GH secretion. Failure to suppress the GH level to below 0.4 µg/l is diagnostic of acromegaly. Individuals with type 1 diabetes commonly exhibit GH hypersecretion [9] (Figure 22.3), which in turn may reflect GH resistance and the reduced effect of GH to stimulate IGF-I secretion in the liver, resulting in circulating IGF-I levels in the lower normal range (Figure 22.4). Accordingly, an increased circulating IGF-I level above the normal range is a strong diagnostic indicator of acromegaly in type 1 diabetes. The elevated GH levels in type 1 diabetes return to normal with improved glycaemic levels.

Biochemical diagnosis (or suspicion) of acromegaly provides the indication for magnetic resonance (MR) imaging of the anterior pituitary to detect and measure the size of the adenoma (Figure 22.1).

Treatment of acromegaly involves surgery, medical therapy, and in rare therapy-resistant cases radiotherapy (Table 22.2) [3]. A conservative observational strategy may be applied in individuals with acromegaly if the risks of treatment side effects and/or complications exceed the expected beneficial effects on symptoms. Transsphenoidal surgery is first-line therapy of a macroadenoma, rapidly lowering GH levels and reducing any increased pressure on the optic chiasm, subsequently resulting in reduced symptoms including improvements of affected visual fields. However, due to the macroadenoma's large size, commonly extending beyond the pituitary fossa, surgery is only curative in around 40–50% of individuals with macroadenomas [12]. In contrast, cure is achievable in more than 85% of individuals with microadenomas [12].

Once-monthly injection of the somatostatin analogues, octreotide long-acting release (octreotide-LAR) and lanreotide, is first-line medical therapy, which lowers circulating GH and normalizes IGF-I levels in 30–50%, and is associated with a reduction in tumour volume in ~60% of individuals with acromegaly [1, 13, 14]. In some cases, increasing doses and/or reduced dose interval may improve clinical and biochemical response. The primary side effects are gastrointestinal, but with neutral long-term impact on glucose tolerance.

Oral octreotide was recently approved in the USA as long-term treatment. Pasireotide is a novel and more potent somatostatin analogue, which primarily inhibits somatostatin receptor type 5 (SST5). The use of pasireotide is associated with a high prevalence of hyperglycaemia (70%) and overt diabetes in up to 40% of individuals with acromegaly, due to inhibition of insulin secretion [15].

Oral treatment with the dopamine agonist cabergoline has only a modest effect on GH secretion in a limited number of individuals

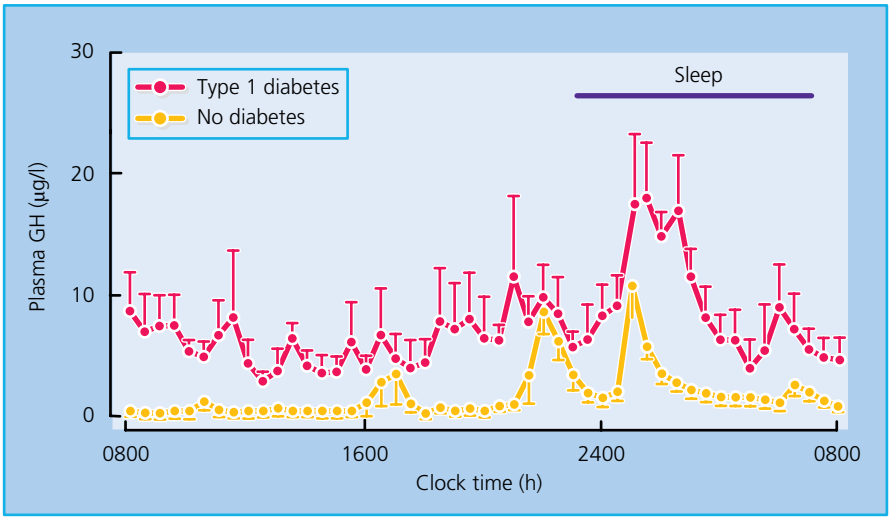


Figure 22.3 Increased growth hormone (GH) secretion in type 1 diabetes. Note the marked hypersecretion during sleep in the early hours of the morning. Source: Hansen et al. 1970 [10]. Reproduced with permission of John Wiley & Sons.

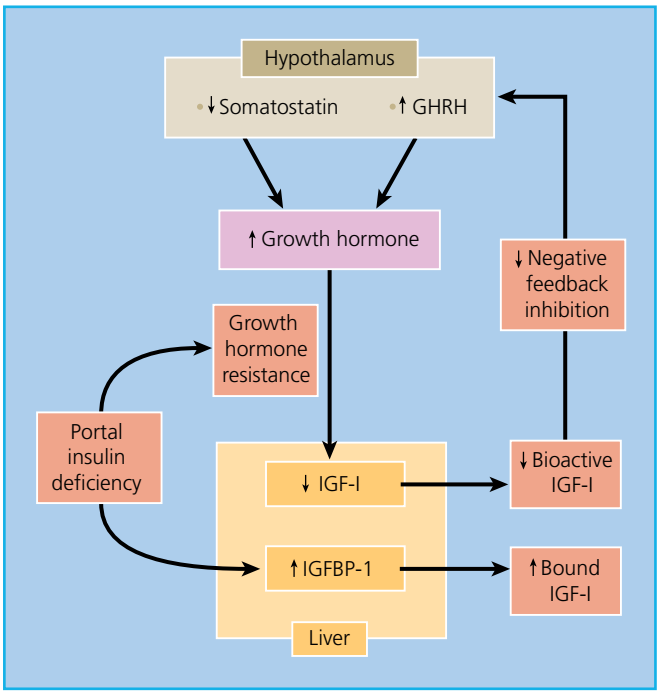


Figure 22.4 Mechanisms of growth hormone (GH) hypersecretion in diabetes. Insulin-like growth factor binding protein 1 (IGFBP-1) binds and reduces the bioavailability of insulin-like growth factor I (IGF-I), which normally decreases GH secretion by negative feedback inhibition on the hypothalamus and pituitary; IGFBP-1 expression is inhibited by insulin. GHRH, growth hormone–releasing hormone.

Table 22.2 Treatment of acromegaly.

Advantages	Disadvantages
Transsphenoidal surgery	
Rapid effect	Invasive, requires general anaesthetic
Can restore vision in optic nerve compression	Non-curative for large extrasellar tumours
Might be curative if complete resection	
Somatostatin analogue drugs	
Non-invasive	Monthly intramuscular injection
May reduce tumour	Expensive
Normal IGF-I in up to 60% of treated individuals	Gastrointestinal side effects (diarrhoea)
	Unlikely to be curative (i.e. continuous therapy needed)
	Hyperglycaemia and overt diabetes (pasireotide)
Pegvisomant	
Non-invasive	Expensive
Blocks GH action	GH concentrations remain elevated
Radiotherapy	
Non-invasive	Slow onset of effect (several years)
Likely to shrink tumour	Standard external three-beam radiotherapy likely to cause hypopituitarism by destroying other pituitary cell types
Likely to reduce GH levels	
Might be curative	

GH, growth hormone; IGF-I, insulin-like growth factor I.
Source: Adapted from Holt and Hanley 2021 [11].

and is rarely sufficient as mono-therapy. Cabergoline may be a useful adjunct co-treatment to surgery and/or somatostatin analogue injection therapy in the ~25% of individuals with acromegaly with co-secretion of prolactin, indicative of increased expression of dopamine receptors in the adenoma [14]. Besides increased suppression of GH secretion, this allows for reduced doses, and therefore reduced costs, as well as fewer of the gastrointestinal side effects associated with use of somatostatin analogues.

As an alternative to GH-lowering treatments, pegvisomant was developed as a GH antagonist preventing GH dimerization, thereby blocking downstream GH signalling. Pegvisomant effectively results in reversing symptoms and clinical features of acromegaly and is associated with a normalization of IGF-I levels in ~60% of all treated individuals after five years of treatment [3, 16, 17]. As a result of reduced negative feedback inhibition, pegvisomant treatment increases circulating GH levels from the somatotroph

adenoma. This, however, is not associated with increased tumour growth, as otherwise seen in bilateral adrenalectomy in Cushing disease (Nelson syndrome) [16, 17].

Radiotherapy is only used as third-line treatment in rare cases with active disease after surgery and medical therapy. Conventional three-field external beam radiotherapy is highly effective in pituitary tumour destruction and lowering of GH and IGF-I levels [3, 18]. Alternatively, if preservation of adjacent normal pituitary tissue and function has a high priority, stereotactic radiotherapy may be applied. Pituitary radiotherapy is associated with increased risk of subsequent cerebrovascular disease, which needs to be considered when deciding between the available treatment options [19].

Glucose tolerance and acromegaly treatment

Glucose tolerance improves in most individuals after successful treatment with normalization of GH levels using pituitary surgery and/or irradiation [20, 21]. Somatostatin analogues decrease insulin secretion and may therefore be associated with transient deterioration of glucose intolerance in some individuals [22, 23]. However, glucose tolerance improves along with lower GH levels during long term somatostatin analogue treatment in most individuals [13]. Insulin sensitivity and glucose tolerance also improve when blocking GH receptor binding with pegvisomant [24, 25]. Post-surgery or radiotherapy, hypopituitarism and GH deficiency may predispose to increased total and central adiposity, which in turn may cause or precipitate insulin resistance and glucose intolerance [8]. Glucose intolerance in individuals treated for or recovering from acromegaly cannot be differentiated from type 2 diabetes.

GH promotes growth including increased vascularization and excessive GH levels have been linked to proliferative diabetic retinopathy. Increased numbers of retinal vessels have been reported in acromegaly [26], and resolution of diabetic retinopathy has been reported in a few individuals with rapid-onset panhypopituitarism [27, 28]. People with diabetes who have GH deficiency only rarely develop retinopathy [29], and a study in mice showed that inhibition of GH secretion ameliorated diabetic retinopathy [30]. Nevertheless, compared with people with diabetes without acromegaly, individuals with both acromegaly and diabetes do not show an increased incidence of diabetic retinopathy [31, 32]. This may be due to the relatively mild or transient phenotypic presentation of diabetes in acromegaly, or alternatively it may reflect that GH is not a strong driver of diabetic retinopathy.

Cushing syndrome

Origin and clinical features

Cushing syndrome is caused by excessive glucocorticoid levels accompanied by characteristic changes of physical appearance, as well as various pathological metabolic and cardiovascular changes (Figure 22.5, Table 22.3) [33–35]. Cushing syndrome along with Cushing disease (Cushing syndrome caused by adrenocorticotropin [ACTH]-secreting corticotroph pituitary adenomas) are named after Harvey Cushing, who was the first to describe the condition(s) in 1912. The commonest cause of Cushing syndrome is the use of synthetic glucocorticoids to treat or prevent conditions with aberrant activation of the immune system as a core part of the disease pathology, such as rheumatoid arthritis, asthma, and chronic obstructive pulmonary disease (COPD). Two-thirds of all cases with Cushing syndrome arising in the context of a non-iatrogenic state are due to excessive ACTH-secreting adenomas of the anterior pituitary, with an incidence rate of 2–3 new cases per million people per year. In ~20% of individuals with endogenous Cushing syndrome, the cause is an adrenal cortex glucocorticoid-secreting tumour, and in 5–10% the cause is ectopic ACTH secretion from a small cell lung carcinoma or from carcinoid tumours [33–36]. Cushing syndrome is three times more common in women than in men, and the characteristic symptoms, physical appearance, as well as increased cardiovascular morbidity and mortality are caused directly by prolonged excessive cortisol levels and tissue exposure. Cortisol is the predominant glucocorticoid hormone in humans (Figure 22.5, Table 22.3) [33–36].

Disturbance to glucose tolerance

Overt diabetes is observed in 20–50% of individuals with Cushing syndrome, and up to 70% of cases exhibit some degree of glucose intolerance [35, 37, 38]. Individuals with pre-existing diabetes

Figure 22.5 Cushing syndrome in a woman presenting with glucose intolerance, hypertension, and altered appearance. The original presentation related to subfertility was attributed as polycystic ovarian syndrome. The cause of the glucocorticoid excess was a small adenoma in the right adrenal gland. Six months following its removal by unilateral adrenalectomy, the pronounced changes in physical appearance led to the woman being requested to renew her passport. Blood pressure and glucose homeostasis returned to normal. Source: Courtesy of Professor Neil Hanley and Rachel Jennings, University of Manchester, UK.

Table 22.3 Clinical features of Cushing syndrome.

Easily bruised, thin skin; poor wound healing
Striae (purple or violaceous rather than white)
Thin (osteoporotic) bones that easily fracture
Glucose intolerance/diabetes mellitus
Central obesity, characteristic rounded facies, buffalo hump
Susceptibility to infection
Predisposition to gastric ulcer
Hypertension
Disturbance of menstrual cycle; symptoms overlap with polycystic ovarian syndrome
Mood disturbance (depression, psychosis)

risk factors such as obesity or a family history of diabetes are at the highest risk. As is the case for almost all types of diabetes secondary to hypersecreting endocrine conditions, diabetes in Cushing syndrome is phenotypically indistinguishable from the clinical presentation of type 2 diabetes. Glucocorticoid excess causes both hepatic and peripheral insulin resistance appearing alongside hyperinsulinaemia as a compensatory phenomenon [37]. The increased hepatic glucose production is predominantly caused by increased gluconeogenesis (as opposed to glycogenolysis) [35, 39]. Glucocorticoid excess is associated with increased proteolysis and release of amino acids in muscle, as well as increased lipolysis and release of glycerol and free fatty acids from peripheral adipose tissue depots, which in turn fuel hepatic gluconeogenic enzymes including phosphoenolpyruvate carboxykinase (PEPCK) (Figure 22.6) [39, 40]. Furthermore, glucocorticoids also increase hepatic glycogen storage [41].

Normalization or improvement of carbohydrate metabolism in Cushing syndrome can be obtained with all types of interventions and treatments that successfully reduce cortisol levels. Unfortunately, diabetes or glucose intolerance does not disappear completely in all individuals obtaining remission from Cushing syndrome. The extent to which this is due to some degree of non-reversible changes of insulin secretion or action after long-term cortisol exposure, or whether it may be explained by another diabetes-predisposing condition, is unknown. In cases of Cushing syndrome with acute severe hyperglycaemia, intensive insulin therapy with multiple daily insulin injections is indicated, which may be combined with steroidogenesis inhibitor therapy to obtain a fast reduction of serum cortisol levels. In individuals with Cushing syndrome and less severe degrees of diabetes or glucose tolerance, oral anti-diabetes agents, including insulin-sensitizing drugs such as metformin and peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists, are the drugs of first choice. A recent study reported multiple relevant, beneficial effects of metformin on fibrinolysis, inflammatory markers, carotid intima-media thickness, clinical markers of disease activity, frequency of pneumonia, overall rate of moderate to severe infections, as well as all-cause hospitalization and admissions due to adverse events in individuals on systemic glucocorticoid therapy [42]. Thiazolidinediones increase peripheral adipose tissue lipid storage capacity and reduce visceral fat and have ACTH-lowering effects *in vitro*. However, increased total weight and body fat content, as well as unclear overall cardiovascular risk/benefit ratio, make thiazolidinediones a less attractive choice than metformin. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors may be useful to reduce glucose and weight, and in addition provide increased cardiovascular and renal protection. On the downside, glucocorticoid excess may further increase the risk of urogenital infections with SGLT-2 inhibitor treatment. Glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors may be used to increase glucose-dependent insulin secretion and reduce glucagon secretion, and GLP-1 receptor agonists may also reduce appetite and exhibit favourable effects on fat distribution. Finally,

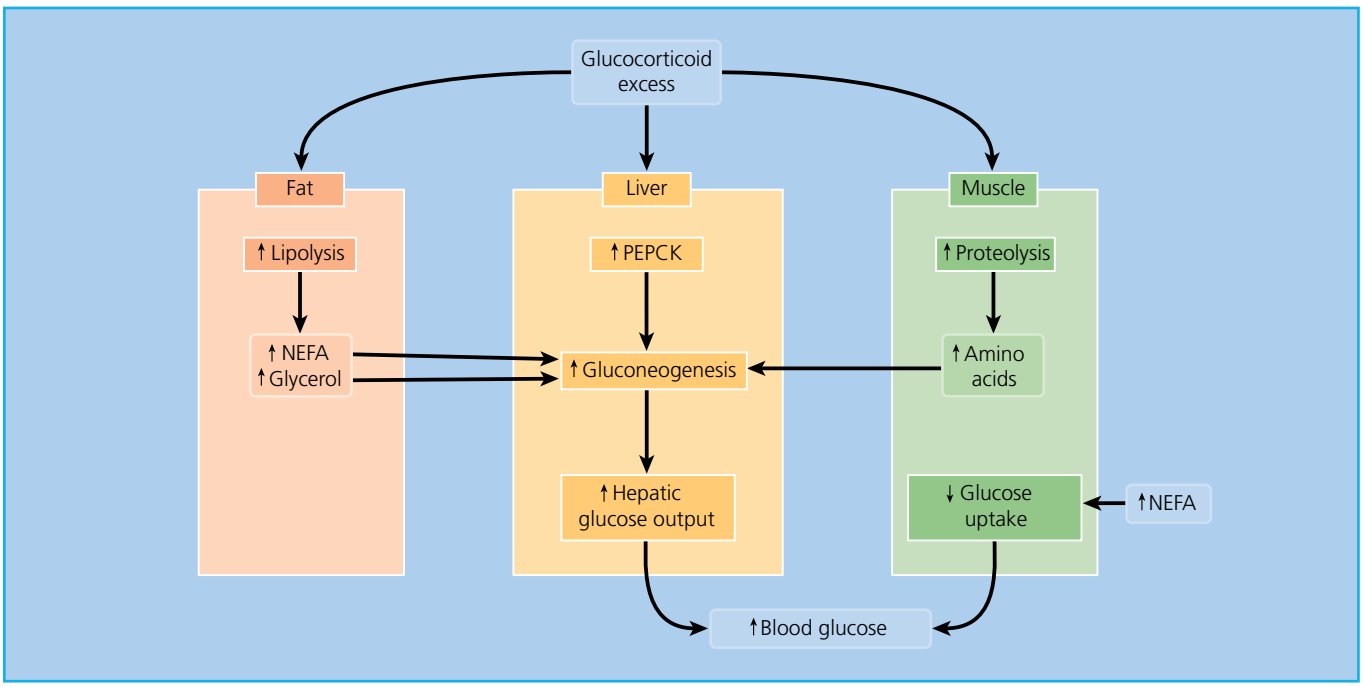


Figure 22.6 Mechanisms of hyperglycaemia and diabetes in Cushing syndrome. NEFA, non-esterified fatty acids; PEPCK, phosphoenolpyruvate carboxykinase.

sulfonylureas may be used, but have in general lost attractiveness compared with modern type 2 diabetes therapies due to inferior long-term effectiveness, weight gain, risk of hypoglycaemia, as well as lack of convincing cardiovascular benefits.

Diagnosis and treatment

Cushing syndrome caused by exogenously administered glucocorticoids is easily diagnosed and treated by reducing the dose of or removing the medication. The earliest symptoms and signs of Cushing syndrome, including fatigue and weight gain, are relatively vague and unspecific, and explain why the diagnosis is often missed or delayed. Accordingly, it is important to consider Cushing syndrome as an underlying cause or differential diagnosis in all individuals with type 2 diabetes. Undiagnosed Cushing syndrome is present in up to 2% of all individuals with type 2 diabetes [43]. A thorough interrogation and objective clinical examination are critical in the diagnosis of Cushing syndrome and clinicians should pay attention to symptoms, such as changes in psychological well-being and proximal myopathy, as well as specific signs such as violaceous stretch marks (*striae*), a round *moon face*, thin extremities in the context of an extended abdomen, and disposition of increased adipose tissue in the neck (*buffalo hump*) [33–35].

With a clinical suspicion of Cushing syndrome, the first goal is to determine the extent to which circulating cortisol levels are increased above normal as a result of uninhibited autonomous secretion [33–35]. Usually, a combination of the available tests is used to ensure sufficient diagnostic accuracy for Cushing syndrome (Table 22.4). Cortisol exhibits clear diurnal variation, with high serum concentrations during the day and low levels at bedtime and night. The midnight serum cortisol level is used as a measure of the extent to which there is a lack suppression of daytime cortisol, implying glucocorticoid excess. Individuals with Cushing syndrome are usually admitted to hospital in quiet surroundings 24 hours prior to testing to avoid artificial high cortisol measurements occurring with even low-stress situations, although increasingly testing may be performed at home. Salivary cortisol measurement may be used and posted by the person from home to the laboratory. However, this requires careful validation of the assay for salivary cortisol measurements, and contamination with blood, for instance from teeth brushing, must be avoided, as salivary cortisol levels are 10-fold lower than in serum. A low-dose dexamethasone suppression test administered at midnight with serum cortisol measurements at 8 a.m. is used to test the physiological negative feedback loop of glucocorticoids suppressing pituitary ACTH secretion. If inconclusive or positive, the low-dose test is followed by the slightly more specific 48-hour dexamethasone suppression test [33]. False-positive tests may occur in individuals with increased dexamethasone metabolism, as seen with antiepileptic medication. Oral contraceptive medication increases the production of glucocorticoid-binding proteins, resulting in artificial high total serum cortisol levels, and should therefore be paused for at least one month prior to serum cortisol measurements. Endogenous cortisol production can also be examined from total cortisol urine excretion as measured over 24 hours, typically over two or three days.

When the suspicion of excessive endogenous cortisol production and Cushing syndrome has been confirmed, different tests are available to determine the underlying aetiology (Table 22.4) [33–35]. Although MR imaging is the state-of-the-art method to visualize a pituitary adenoma, this should not be performed until firm biochemical evidence of a pituitary source of Cushing syndrome has been established. Thus, neither a positive nor a negative finding of a pituitary tumour can be used in isolation to confirm or exclude Cushing disease. Measurement of serum ACTH levels is considered mandatory to determine whether Cushing syndrome is ACTH dependent. A concentration below the detection limit suggests primary adrenocortical cortisol overproduction, with compensatory pituitary suppression of ACTH release. In individuals with detectable or raised cortisol levels above normal, there is a need to exclude ectopic (non-pituitary) ACTH production before the diagnosis of the classic Cushing disease can be made and treatment can be determined. In contrast to ectopic causes of ACTH overproduction, corticotroph pituitary adenomas usually sustain some degree

Table 22.4 Diagnosis of endogenous Cushing syndrome.

Test	Interpretation
Screening tests to diagnose Cushing syndrome	
Midnight serum cortisol or salivary cortisol measurement	Maintained daytime levels at midnight indicates autonomous cortisol production of Cushing syndrome. Normal value <50 nmol/l in a sleeping patient, grey zone 50–138 nmol/l. Cortisol <207 nmol/l in an awake person may exclude Cushing syndrome
1 mg overnight DST. Oral dexamethasone taken at midnight	Serum cortisol <50 nmol/l at following 9 a.m. is considered a normal value
Formal low-dose DST (0.5 mg × 8 doses 6-hourly ending at 3 a.m.)	Serum cortisol <50 nmol/l following 9 a.m. is considered a normal value
24 h urinary free cortisol measurement	Elevated values support diagnosis of Cushing syndrome
Tests to localize cause of cortisol excess	
Serum ACTH measurement	If suppressed, indicates autonomous adrenocortical overproduction of cortisol (e.g. an adrenocortical adenoma)
If serum ACTH detectable	
High-dose dexamethasone suppression test (2 mg × 8 doses 6-hourly ending at 3 a.m.)[a]	Above 50% suppression of 9 a.m. serum cortisol from pre- to post-test indicates anterior pituitary source; <50% suppression indicates extra-pituitary ectopic source of ACTH
Bilateral IPSS[a]	Gradient from inferior petrosal sinus to periphery of >2 : 1 supports anterior pituitary source (test can also incorporate CRH administration; see text)
MRI	Should only be considered once biochemical evidence of pituitary source obtained. Helpful for surgeon in planning trans-sphenoidal surgery

ACTH, adrenocorticotropic hormone; CRH, corticotropin releasing hormone; DST, dexamethasone suppression test; IPSS, inferior petrosal sinus sampling; MRI, magnetic resonance imaging.
[a] Larger centres may progress straight to bilateral IPSS if available and conducted by experienced operators rather than perform a high-dose dexamethasone suppression test.

of negative feedback inhibition by cortisol, which defines the basis for the high-dose dexamethasone suppression test (Table 22.4). Suppression of serum cortisol by at least 50% after the administration of 16 mg dexamethasone in total over 48 hours suggests Cushing disease. Due to lack of negative feedback inhibition, ectopic ACTH production in non-pituitary tumours is in general associated with higher circulating cortisol levels resistant to such degree of suppression during a 16 mg dexamethasone test. The commonest cause of ectopic ACTH production is an aggressive bronchial carcinoma, while a minority is caused by a less severe carcinoid tumour. Binding of ACTH to the type 1 melanocortin receptor (MC1R) leads to increased skin pigmentation, which accordingly is commoner in individuals with ectopic ACTH production compared with other causes of Cushing syndrome.

Bilateral inferior petrosal sinus sampling (IPSS) is a more sensitive as well as specific diagnostic procedure to differentiate between pituitary versus ectopic ACTH overproduction. In this test, central (sinus petrosis) and peripheral (venous) ACTH levels are measured simultaneously before and after intravenous injection of 100 µg corticotropin-releasing hormone (CRH). The finding of a central versus peripheral baseline ACTH gradient of at least 2 : 1, or of 3 : 1 after the CRH injection, is consistent with pituitary ACTH overproduction. IPSS may furthermore help lateralize a pituitary adenoma by identifying clear differences in ACTH levels between right and left sinuses. IPSS is associated with increased thrombosis risk (affecting around 1% of procedures) and is therefore a procedure restricted to endocrine clinics with high expertise.

In Cushing syndrome with a primary suspicion of ectopic ACTH production, various imaging technologies are used to screen for tumours, including computerized tomography (CT), MR imaging, and/or somatostatin receptor isotope scintigraphy. Somatostatin receptors are detectable in around two-thirds of ACTH-secreting carcinoid tumours. Adrenal cortex tumours with high lipid contents (indicative of increased steroid production) can be detected with abdominal CT or MR imaging.

Due to the severe symptoms, complications, and comorbidity of Cushing syndrome [33–35], curative treatment approaches always have the highest priority. Unilateral adrenalectomy is the preferred treatment option in individuals with a primary adrenocortical source of cortisol overproduction. Surgery may be curative in some individuals with ectopic ACTH-secreting carcinoid tumours, whereas the overall severity and poor prognosis in individuals with ACTH overproduction from a bronchial carcinoma commonly make palliative care the right choice. Trans-sphenoidal removal of the corticotroph adenoma is the first-line treatment in individuals with established Cushing disease. Trans-sphenoidal surgery is curative in approximately two-thirds of individuals with Cushing syndrome, due to ACTH-secreting adenomas more often being microadenomas. Indications, side effects, and risks of radiotherapy in Cushing disease resemble those described for acromegaly.

Currently medical treatments are generally inferior to surgery and therefore remain second-line treatments in Cushing syndrome and Cushing disease. However, several new drugs are under investigation, and medical therapy is therefore gradually gaining increased importance. Pharmacological suppression of adrenocortical steroidogenesis with ketoconazole or metyrapone has been used to relieve symptoms and improve glucose homeostasis temporarily if surgery is delayed [33, 34]. However, long-term experience with these drugs is limited due to efficacy and safety concerns. Metyrapone is currently under investigation in a large international multicentre trial to establish its efficacy and safety more broadly in Cushing syndrome.

Most corticotroph adenomas express various somatostatin receptor subtypes at their surface, and treatment with the somatostatin multiligand analogue pasireotide provides effective lowering of pituitary ACTH secretion, as well as serum and urinary cortisol levels, in people with Cushing disease. Pasireotide administered either twice daily subcutaneously or once monthly intramuscularly using an LAR formulation is an effective as well as safe long-term treatment in Cushing disease [44, 45]. However, inhibition of somatostatin receptors in gut and pancreas simultaneously blocks the secretion of incretin hormones and insulin, resulting in the development of glucose intolerance in more than 70% of individuals on pasireotide treatment [44, 46]. Close monitoring of glucose is therefore imperative in individuals on pasireotide treatment [47]. Osilodrostat and levoketoconazole are novel steroidogenesis inhibitor agents with mechanisms of action resembling metyrapone and ketoconazole, respectively, currently under investigation for Cushing disease. Among novel glucocorticoid receptor-directed or antagonist drugs under development, mifepristone and relacorilant both have promising effects on blood pressure and glucose metabolism, and there is an unexplored future potential in combining current and new therapies with different modes of action in Cushing disease.

In a small fraction of therapy-resistant individuals, bilateral adrenalectomy provides a rapid resolution of excessive cortisol secretion. However, total loss of negative feedback inhibition of pituitary ACTH secretion can result in treatment-refractory pituitary tumour growth with severe adverse local pressure effects, including visual impairments and panhypopituitarism (Nelson syndrome). Adjunct radiotherapy directed against the anterior pituitary gland can be used to prevent or treat individuals with imminent or overt Nelson syndrome.

Glucose tolerance following treatment of Cushing syndrome

Most individuals with Cushing syndrome improve or fully regain their adrenal cortisol production within weeks to months after successful trans-sphenoidal surgery. Nevertheless, long-term suppression of normal corticotrophs (pituitary or ectopic ACTH-secreting tumours), or of adrenocortical cells (cortisol-secreting tumours), is associated with secondary degenerative changes in the remaining normal endocrine tissue. This causes a state of hypocortisolism and all individuals with Cushing disease will need exogenous glucocorticoid substitution after trans-sphenoidal surgery. The need for exogenous glucocorticoids is highest in the period immediately after surgery due to the acute stress situation and because the body needs time to adjust from the situation of excessive endogenous cortisol exposure. A large proportion of individuals will never fully recover a normal diurnal adrenal function [47] and will require lifelong exogenous glucocorticoid substitution.

Insulin action and glucose tolerance improve rapidly after successful treatment of Cushing syndrome (Figure 22.5). Prescribed anti-diabetes treatments therefore require careful monitoring and adjustment during and after pituitary surgery. Care needs to be taken to avoid hypoglycaemia when reducing the total glucocorticoid exposure after surgery, especially among those individuals who are dependent on replacement doses of hydrocortisone. Conversely, other individuals will need continued care and treatment for diabetes due to persistent changes in body composition

and features of the metabolic syndrome [40]. A study reported persistent visceral obesity and glucose intolerance in ~60% of individuals who fulfilled criteria for remission of Cushing syndrome [48].

Phaeochromocytoma and paraganglioma

Epidemiology, clinical features, and genetics

Catecholamine-secreting phaeochromocytomas and paragangliomas are tumours arising from the neural crest–derived chromaffin cells of the adrenal medulla (phaeochromocytoma, 80–85%) (Figure 22.7) [49, 50] or from the paravertebral sympathetic chains in the chest, abdomen, or pelvis (paragangliomas). Approximately 10% of phaeochromocytomas are bilateral. They can secrete epinephrine, norepinephrine, dopamine, or various combinations thereof. Around 40% of phaeochromocytomas and paragangliomas occur on a hereditary basis either as part of syndromes such as MEN2, von Recklinghausen neurofibromatosis, or von Hippel–Lindau disease [51], or as the single disease manifestation of known mutations in at least 17 known genes [52] (Table 22.5). For instance, succinate dehydrogenase subunit B (*SDHB*) and succinate dehydrogenase subunit D (*SDHD*) mutations are more frequent in extra-adrenal tumours [51, 52], and mutations in *SDHB* are more commonly associated with a malignant phenotype [51, 52]. The risk of malignancy also increases with tumour size [51, 52].

The clinical symptoms of catecholamine-secreting phaeochromocytomas and paragangliomas are classically described as a triad: headaches, sweating, and tachycardia [53, 54]. Hypertension is the commonest clinical finding and occurs in 80–90% of cases. It can be paroxysmal or sustained, the latter occurring especially in children and in norepinephrine-secreting tumours [55]. Other symptoms may be secondary to the co-secretion of various other peptide hormones such as vasoactive intestinal peptide (VIP), substance P, atrial natriuretic factor, endothelin-1, CRH, and GHRH [55]. The normal adrenal medulla predominantly secretes epinephrine, converted from norepinephrine by methylation. This reaction is governed by the adrenal specific enzyme phenylethanolamine-*N*-methyltransferase (PNMT), the expression of which is dependent on high concentrations of cortisol draining centripetally from the outer adrenal cortex towards the adrenal vein [53]. For this reason, larger tumours with more marked disturbance of the normal anatomy or paragangliomas along the sympathetic chain are notable for predominantly secreting norepinephrine as conversion to epinephrine is compromised.

Glucose intolerance

Approximately 50% of individuals with phaeochromocytomas and paragangliomas exhibit various degrees of glucose intolerance, with ~16% of individuals having overt diabetes [56]. Diabetes is more common in phaeochromocytomas than in paragangliomas. The presence of both hypertension and diabetes in a young person of normal

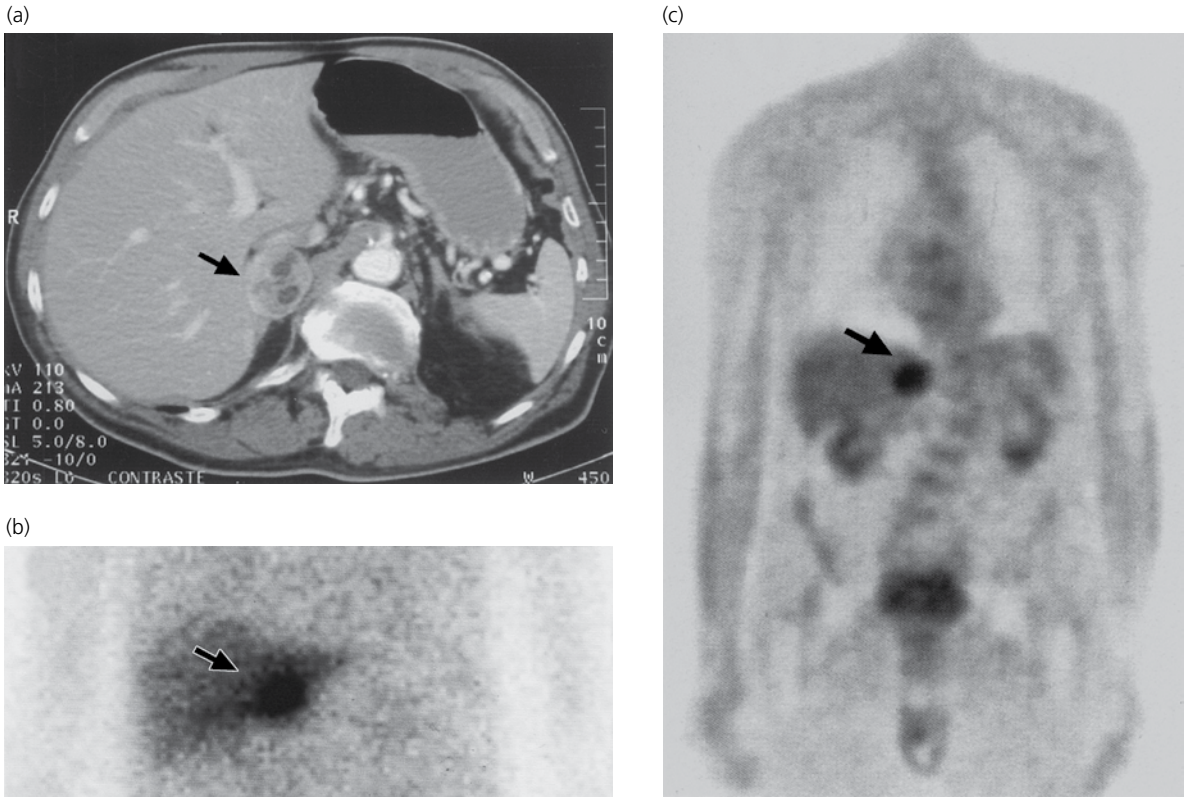


Figure 22.7 Phaeochromocytoma in a 75-year-old man with recent-onset type 2 diabetes treated with a sulfonylurea, who was admitted on an emergency basis with severe chest pain and hypertension (blood pressure 240/130 mmHg). Blood glucose on admission was 27 mmol/l. Urinary catecholamine excretion was greatly increased, and a phaeochromocytoma of the right adrenal was demonstrated by (a) computed tomography; (b) scanning with ^{131}I-metaiodobenzylguanidine, which is taken up by catecholamine-synthesizing tissues; and (c) positron emission tomography with 18 F-fluorodeoxyglucose. After laparoscopic removal of the tumour, diabetes and hypertension both resolved. Source: Courtesy of Professor Neil Hanley and Rachel Jennings, University of Manchester, UK.

Table 22.5 Genes associated with catecholamine-secreting phaeochromocytomas and paragangliomas.

Gene	Germline mutation rate (% detected in all PPGL)	Key characteristics and associations
SDHB	10.3	Extra-adrenal tumours; malignant phenotype
SDHD	8.9	Extra-adrenal tumours; paternal inheritance
VHL	7.3	von Hippel–Lindau disease
RET	6.3	Multiple endocrine neoplasia type 2
NF1	3.3	Neurofibromatosis type 1
TMEM127	<2	Adrenal tumours
SDHC	1	Head and neck PGL
SDHA	<2	Extra-adrenal tumours
SDHAF2	<2	Head and neck PGL
MAX	<2	Malignant phenotype
MDH2	<2	Multiple tumours; thoracic and abdominal PGL
PHD1	<2	Multiple tumours; early-onset polycythaemia
GOT2	<2	Multiple thoracic and abdominal PGL
IDH3	<2	Head and neck PGL; acute myeloid leukaemia
SLC25A11	<2	Thoracic and abdominal PGL
DNMT3A	<2	Head and neck PGL; acute myeloid leukaemia
DLST	<2	Multiple thoracic and abdominal PGL

PGL, paraganglioma; PPGL, phaeochromocytoma and paraganglioma.

body weight should raise suspicion of phaeochromocytoma and paraganglioma. Catecholamines, together with GH and glucocorticoids, belong to the class of *glucose counter-regulatory hormones* that impair insulin action and secretion (Figure 22.8) [57–59]. Epinephrine inhibits insulin secretion via stimulation of α_2-adrenergic receptors on pancreatic β cells [60]. In the liver, epinephrine stimulates β_2-adrenoceptors to enhance glycogenolysis transiently and gluconeogenesis in a more sustained fashion [61–63].

Hepatic gluconeogenesis is fuelled by the precursors lactate, alanine, and glycerol, which in turn are partly generated by β_2-adrenergic stimulation of muscle and adipose tissue lipolysis. Lipolysis in adipose tissue is also stimulated via the β_1- and β_3-adrenoceptors. To this end, epinephrine can impair glucose utilization in muscle through direct β_2-adrenergic effects. The predominance of these β_2-adrenergic effects probably explains why epinephrine, with its higher affinity for β_2-receptors, is more potent than norepinephrine in producing hyperglycaemia [61–63]. Activation of epinephrine release is an important component in correcting hypoglycaemia, following inhibition of insulin and increased glucagon secretion, in the hierarchy of counter-regulatory responses (Chapter 40).

Diagnosis and treatment

Phaeochromocytomas and paragangliomas are diagnosed by demonstrating an excess of circulating catecholamines. This is most accurately achieved by measuring their metabolites, metanephrines, derived by the enzymatic action of catechol-O-methyl transferase in the urine over 24 hours or more commonly in the plasma [49]. These measures are superior to historical measurement of the metabolite, vanylmandelic acid, and the catecholamines themselves in terms of sensitivity and specificity [49]. Imaging the tumour can be performed by either MR or CT. Treatment is surgical removal of the tumour as an adrenalectomy, increasingly performed laparoscopically unless malignancy is suspected [49]. Preoperative preparation must be meticulous to prevent both a hypertensive crisis during manipulation of the tumour and cardiovascular collapse after its removal. This is achieved by initial α-receptor blockade, most commonly using the irreversible agent phenoxybenzamine, followed by a β-blocker if needed. The order of implementation is important to prevent a hypertensive crisis from unopposed α-adrenoceptor stimulation. The preoperative α-adrenergic blockade often controls hypertension, but has less effect on glucose intolerance [61, 64]. In malignant phaeochromocytoma where surgery is not possible, adrenolytic drugs, such as mitotane, can be used palliatively.

Glucose tolerance in response to treatment of phaeochromocytomas and paragangliomas

Removal of the tumour in most cases also corrects the metabolic abnormalities, including hypertension and glucose intolerance [61, 64–66]. Clinical genetics input to guide treatment, diagnosis of comorbidities, follow-up, as well as identifying which family members should be screened, is important and required in all individuals, even in seemingly isolated tumours [49, 51]. Hyperparathyroidism and MEN1 can be excluded simply by measuring serum calcium and parathyroid hormone. Annual measurements of plasma metanephrines are required after surgery to exclude recurrent phaeochromocytomas and paragangliomas.

Glucagonomas

Glucagonomas are tumours derived from the α cell of the pancreatic islet that, along with somatostatinomas and VIP-producing tumours (VIPoma), represent a rare group of hypersecreting gastroenteropancreatic endocrine tumours associated with glucose intolerance or diabetes. Glucagonomas may occur sporadically or as part of the MEN1 syndrome caused by mutations in the tumour suppressor gene, *MENIN* [67]. The most striking clinical features of excessive glucagon secretion (the *glucagonoma syndrome*) are weight loss, necrolytic migratory erythema, diabetes, cheilosis or stomatitis, and diarrhoea [68]. Necrolytic migratory erythema is recognized as an intermittent blistering rash that spreads across the skin, usually involving the skin around the mouth, buttocks, groin, thighs, as well as distal extremities [69, 70] (Figure 22.9a). Hyperglucagonaemia may contribute to the rash, as may hypoaminoacidaemia through glucagon's enhancement of amino acid uptake by the liver and zinc deficiency [70]. The glucagonoma syndrome is also characterized by a normochromic normocytic anaemia, a tendency to thrombosis (pulmonary embolism is a common cause of death), and neuropsychiatric disturbances [69].

Approximately three-quarters of individuals with glucagonoma have overt diabetes [69], which is explained by glucagon's effect to enhance net hepatic glucose production through increased gluconeogenesis and glycogenolysis [70]. The degree of hyperglycaemia in people with glucagonomas is usually mild and in most cases responds to oral anti-diabetes drugs, although insulin treatment may be required in the most severe cases [69]. Reasons for the relatively mild degree of diabetes in individuals with glucagonoma

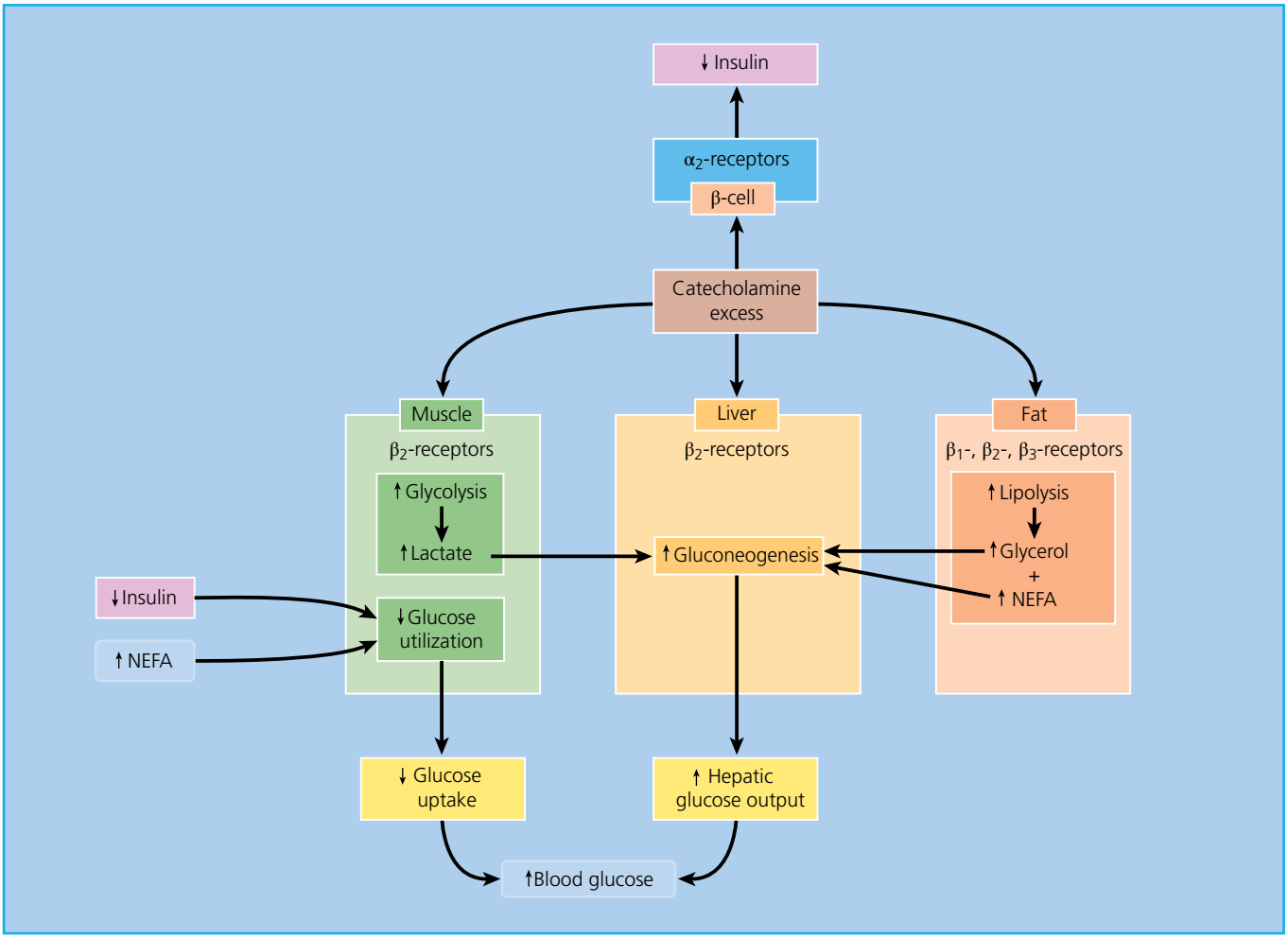


Figure 22.8 Mechanisms of hyperglycaemia in phaeochromocytoma. NEFA, non-esterified fatty acid.

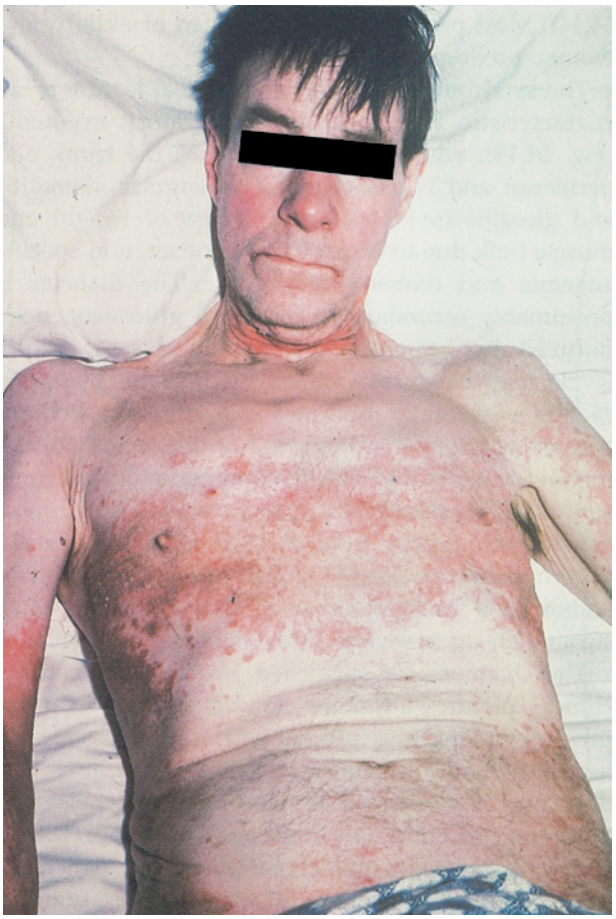
include a diminished effect of glucagon to increase hepatic glucose production with time, as well as compensatory hyperinsulinaemia partly brought about by glucagon's paracrine effect to stimulate insulin secretion in the pancreatic β cells [71]. Differential post-translational processing of tumour-derived proglucagon may lead to concomitant or even predominant overexpression and secretion of other proglucagon-derived peptides, including GLP-1, GLP-2, glicentin, and oxyntomodulin. This, in turn, may cause different gastrointestinal as well as general symptoms including hypoglycaemia [72].

The diagnosis is suggested by the symptoms of the glucagonoma syndrome, particularly the combination of weight loss, a blistering rash, and diabetes. Visualization of an increased pancreatic mass and high fasting plasma glucagon concentration strengthen the diagnosis. However, other causes of hyperglucagonaemia such as severe stress, hepatic and renal failure, hyperglycaemia, small-bowel malabsorption, and synthetic androgenic drugs needs to be excluded [69, 70, 74]. The treatment of first choice is surgery; however, 50% of tumours have metastasized to the liver by the time of diagnosis (Figure 22.9b), limiting the options for cure [68]. Supplementary treatment options include embolization of the hepatic artery, chemotherapy, and/or use of somatostatin analogues to suppress glucagon secretion. The rash usually disappears when glucagon levels are normalized. Additional symptomatic treatments include administration of zinc and/or a high-protein diet [68–70, 73].

Somatostatinomas

Somatostatinomas are extremely rare tumours arising in 1 in 40 million individuals from δ cells of the pancreatic islet or enteroendocrine cells of the duodenum and ampulla of Vater [74]. Somatostatinomas may occur sporadically or as part of genetic syndromes including MEN1, neurofibromatosis type 1 (*NF1* gene with malfunction of RAS/MAPK pathway), or Pacak-Zhuang syndrome (*EPAS1* gene encoding HIF) [74–76]. Somatostatin has widespread inhibitory effects on endocrine and exocrine secretory functions in the gastroenteropancreatic system [77], explaining the symptoms and clinical findings in individuals with somatostatinomas, which include diabetes, steatorrhoea, gallstones, and hypochlorhydria [75]. Dual inhibition of insulin and glucagon secretion explains why hyperglycaemia is usually mild and non-ketotic, and why some individuals may even present with hypoglycaemia rather than hyperglycaemia [75]. Insulin treatment is rarely required.

(a)



(b)

Figure 22.9 Glucagonoma showing characteristic necrolytic migratory erythema (a) and multiple hepatic metastases (b). This man had non-ketotic diabetes, managed with low dosages of insulin; the rash recurred many times despite treatment with somatostatin analogue. He died from pulmonary embolus. Source: Courtesy of Professor Stephen Bloom, Imperial College School of Medicine, London, UK.

Diagnosis is suspected by the symptoms described, and further investigated by measuring circulating somatostatin levels. Visualization of the tumour is by CT or MR imaging, or octreotide scintigraphy, subsequently followed by a biopsy. Surgical resection is usually curative when tumours are small and without metastasis [74]. Supplementary or adjunct treatment options in non-radically operated individuals include debulking, embolization, and/or chemotherapy (including radiolabelled somatostatin analogues) [74].

Vasoactive intestinal peptide-producing tumours

Verner and Morrison first reported a clinical case of a VIP-secreting tumour in 1958 [78]. The classic symptoms of Verner–Morrison syndrome caused by increased circulating VIP levels include watery diarrhoea (pancreatic cholera), hypokalaemia, and achlorhydria [73, 79]. Hypercalcaemia and glucose intolerance occur in half of the individuals, but overt diabetes is unusual. Unlike glucagonomas and somatostatinomas, the physiological explanation for hyperglycaemia in VIPomas is unknown, but may be secondary to the glycogenolytic effect of VIP and/or hypokalaemia, which can impair both insulin secretion and insulin sensitivity. VIPomas usually are large and have metastasized at the time of diagnosis, suggesting that the explanation may be less specific and stress related, and thus more likely to be categorized with the type of unspecific diabetes occurring secondary to multiple types of non-endocrine cancers [1]. Diagnosis is obtained by measuring circulating VIP levels, and the treatment of choice is debulking surgery [79].

Hyperthyroidism

Hyperthyroidism is defined by increased production and circulating levels of thyroid hormones, whereas the state of thyrotoxicosis represents the clinical manifestation of hyperthyroidism (Table 22.6) [80, 81]. Autoimmune hyperthyroidism (Graves' disease) is associated with an increased risk of type 1 diabetes, but thyrotoxicosis *per se* is more associated with impaired glucose tolerance in approximately one-third of individuals [82]. The hypermetabolic state of hyperthyroidism causes or worsens hepatic and peripheral insulin resistance, subsequently unmasking glucose intolerance, particularly in people with a pre-existing risk factor, such as obesity or a family history of diabetes [83]. Similarly, hyperthyroidism worsens glucose levels in people with

Table 22.6 Clinical features of thyrotoxicosis plus features associated with Graves' disease.

Clinical features of thyrotoxicosis
Weight loss despite full, possibly increased, appetite
Tremor
Heat intolerance and sweating
Agitation and nervousness
Palpitations, shortness of breath/tachycardia ± atrial fibrillation
Glucose intolerance
Amenorrhoea/oligomenorrhoea and consequent subfertility
Diarrhoea
Hair loss
Easy fatigability, muscle weakness, and loss of muscle mass
Rapid growth rate and accelerated bone maturation (children)
Specific features associated with Graves' disease
Bruit in a diffuse, firm goitre
Thyroid eye disease, also called Graves' orbitopathy
Pretibial myxoedema – thickened skin over the lower tibia
Thyroid acropachy (clubbing of the fingers)
Other autoimmune features (e.g. vitiligo)

pre-existent diabetes [84]. Hypothyroidism is associated with faster intestinal absorption, contributing to increased postprandial plasma glucose levels [59]. Conversely, restoration of euthyroidism rapidly improves or normalizes glucose metabolism [82]. Guidelines for the use of diabetes treatments in individuals with hyperthyroidism do not differ from conventional treatment of type 1 diabetes and type 2 diabetes.

Primary hyperaldosteronism

Primary hyperaldosteronism was first described first by Conn in 1955 and is characterized by hypertension, hypokalaemia, and neuromuscular symptoms [53]. Benign adrenocortical secreting aldosterone adenomas account for ~65% of cases, whereas bilateral hyperplasia accounts for 30% of cases of primary hyperaldosteronism. Glucose intolerance occurs in ~50% of individuals with primary hyperaldosteronism, whereas overt diabetes is rare [85]. As for suspected pathogenic mechanisms, low serum potassium levels are associated with impaired insulin secretion, while elevated aldosterone levels is associated with reduced peripheral insulin sensitivity [65]. Removal of the adenoma or potassium loading increase insulin secretion and normalise glucose metabolism [85].

Primary hyperparathyroidism

Primary hyperparathyroidism characterized by hypersecretion of parathyroid hormone may occur as a result of a parathyroid adenoma or less frequently due to parathyroid hyperplasia [86]. Increased intracellular calcium levels cause insulin resistance and reduced cellular glucose uptake [87], explaining the approximately threefold higher prevalence of diabetes in individuals with more severe degrees of primary hyperparathyroidism compared with the general population [87–89]. The extent to which parathyroidectomy normalizes glucose tolerance is less clear for primary hyperparathyroidism compared with most other types of diabetes secondary to hypersecreting endocrine disorders [90,91]. Treatment of diabetes in individuals with hyperparathyroidism does not differ from general diabetes treatment recommendations.

Polycystic ovarian syndrome

Polycystic ovarian syndrome (PCOS) qualifies as a hypersecreting endocrine disorder through its definition as a clinical or biochemical state of hyperandrogenism in women with oligo- or anovulation, in which other more distinct causes such as Cushing syndrome have been excluded [92,93] (Figure 22.10). The prevalence of PCOS in women of reproductive age is 5–10% and is characterized primarily by hyperinsulinaemia and insulin resistance [93,94]. Approximately 40% of women with PCOS have impaired glucose tolerance and up to 10% overt type 2 diabetes [94]. The risk of PCOS is closely associated with increased obesity, but PCOS also occurs among normal-weight women [93]. Indeed, lifestyle intervention with weight loss represents the treatment of first choice in PCOS women.

Primary hyperinsulinaemia, even to a level higher than required to compensate for the ambient degree of insulin resistance, is likely to take centre stage for the development of PCOS [95]. The raised insulin levels are subsequently the key driver of increased androgen production by both the ovary and the adrenal cortex [96,97]. PCOS is a diagnosis of exclusion, in the sense that clinical and biochemical findings are only supportive of the diagnosis [98]. Increased serum levels of luteinizing hormone (LH) relative to follicle-stimulating hormone (FSH) levels (e.g. the LH : FSH ratio), as well as increased circulating androstenedione and testosterone concentrations, are among the key diagnostic criteria. Serum oestradiol is detectable and usually >200 pmol/l, whereas serum sex hormone–binding globulin (SHBG) levels are usually low. Ovarian ultrasound is indicated to exclude the presence of an androgen-producing tumour [98]. In addition to lifestyle intervention, metformin is indicated in PCOS women both with and without glucose

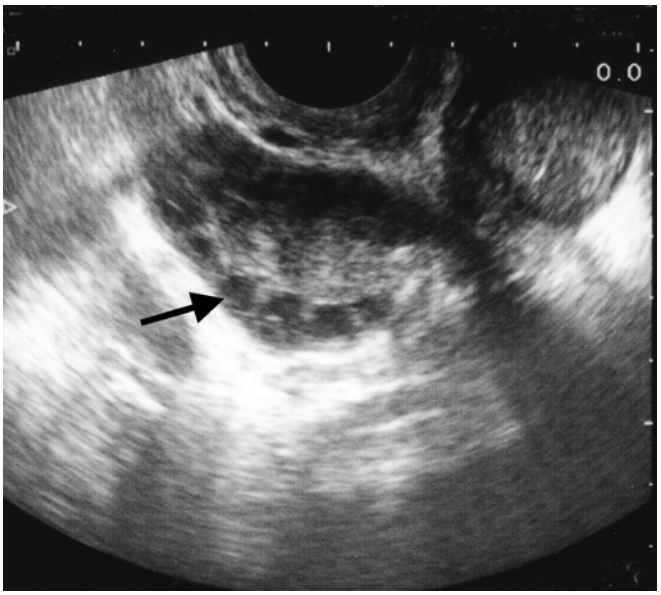


Figure 22.10 Polycystic ovary syndrome, showing characteristic ultrasonographic appearance of large, mainly peripheral cysts (arrow).

intolerance to improve insulin action, lower circulating insulin levels, and eventually to improve menstrual regularity and increase the chance of ovulatory cycles [99]. Other anti-diabetes agents that improve insulin action and/or reduce weight, including GLP-1 receptor agonists, SGLT-2 inhibitors, as well as thiazolidinediones, improve clinical symptoms [100, 101].

Glucose intolerance in hyposecreting endocrine disorders

Although diabetes is much more common in hypersecreting endocrine disorders, the inverse scenario of increased prevalence of diabetes in individuals with hyposecreting endocrine disorders is not uncommon. Thus, both subclinical and overt hypothyroidism is associated with an increased prevalence of diabetes, and to some extent with an increased prevalence of diabetes complications [102, 103]. The mechanisms underlying the link between hypothyroidism and diabetes are less clear than for diabetes and hyperthyroidism, but reduced tissue blood flow, glucose uptake, and insulin clearance have been proposed to play a role [77, 104]. Hypothyroidism has also been linked with an increased risk of hypoglycaemia [105], and the increased prevalence of diabetes in hypothyroidism may to some unknown extent be explained by physical inactivity, weight gain, and/or elevated plasma triglycerides.

Although GH excess is a recognized cause of insulin resistance, increased hepatic glucose production, and diabetes, long-standing GH deficiency is also associated with insulin resistance and increased risk of diabetes [106, 107]. Increased insulin resistance in adults with GH deficiency is largely explained by changes in body composition, with increased total and abdominal fat mass at the expense of reduced lean body mass [107]. GH is a potent activator of adipose tissue lipolysis, and the changes in body composition are therefore readily explained by long-term relative or absolute understimulation of adipose tissue lipolysis. The delicate homeostatic balance between GH's diabetogenic and anti-diabetogenic effects may also explain the conflicting outcomes of long-term GH substitution on glucose tolerance in individuals with GH deficiency [108–112]. Accordingly, there is general consensus that individuals on GH therapy need regular monitoring of glucose metabolism to avoid overtreatment and development of overt diabetes [106, 112].

Other endocrine disorders associated with diabetes

Type 1 diabetes is an autoimmune disease with common or overlapping aetiology and pathophysiological mechanisms with diseases such as Addison disease (autoimmune adrenalitis) and autoimmune thyroid disease. Accordingly, clinicians need to consider the onset of new autoimmune pathology in people with these disorders. In individuals with type 1 diabetes, screening can be justified to exclude hyperthyroidism or hypothyroidism by measuring serum thyroid-stimulating hormone (TSH) annually. The development of Addison disease in people with type 1 diabetes markedly increases insulin sensitivity such that unanticipated hypoglycaemia may occur despite reduced dose requirement. Rare conditions resembling type 1 diabetes with associated endocrinopathies may occur, such as the autoimmune polyglandular syndromes or POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin abnormalities) syndrome. Monogenic causes of diabetes may affect other endocrine organs. Examples (and their respective endocrine disorder) include the various types of haemochromatosis (primary hypogonadism), Wolfram syndrome (diabetes insipidus), and Kearns–Sayre syndrome (hypoparathyroidism, hypogonadism, and hypopituitarism).

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23 Pancreatic Disease and Diabetes

Ranjit Unnikrishnan[1,2] and Viswanathan Mohan[1,2]

[1] Dr. Mohan's Diabetes Specialities Centre, IDF Centre of Excellence in Diabetes Care, Chennai, India

[2] Madras Diabetes Research Foundation, ICMR Center for Advanced Research on Diabetes, Chennai, India

Key points

- Pancreatic disease is a rare cause of diabetes.
- Acute pancreatitis is associated with transient hyperglycaemia that rarely persists.
- Chronic pancreatitis secondary to any cause can lead to permanent diabetes that is typically difficult to manage; imaging studies reveal dilated ducts and pancreatic calculi.
- Tropical calcific pancreatitis is a disease of unknown aetiology found in low- and middle-income countries associated with large pancreatic calculi and diabetes (fibrocalculous pancreatic diabetes).
- Hereditary haemochromatosis is an inherited disorder that produces diabetes secondary to iron deposition in the pancreatic islets and subsequent islet cell damage.
- Pancreatic carcinoma may complicate type 2 diabetes, diabetes secondary to chronic pancreatitis, and, most commonly, fibrocalculous pancreatic diabetes. It is important to suspect malignancy in any person who complains of back pain, jaundice, or weight loss in spite of optimal glycaemic levels.
- Pancreatic surgery can lead to diabetes that is insulin requiring and often difficult to manage.
- Cystic fibrosis is a relatively common genetic disorder affecting the lung, pancreas, and other organs. Up to 75% of adults with cystic fibrosis have some degree of glucose intolerance, and the prevalence of cystic fibrosis diabetes is increasing in parallel with the improved survival of people with cystic fibrosis.

The pancreas plays an important role in carbohydrate metabolism and is a key player in the pathophysiology of the different types of diabetes. It is therefore surprising that pancreatic disease is a rare cause of diabetes, accounting for less than 0.5% of all cases of diabetes. The prevalence of undiagnosed disease, however, may be much higher [1]. The rarity of diabetes in pancreatic disease may be explained, in part, by the presence of considerable β-cell reserve in most individuals. It has been estimated that nearly 80–90% of the pancreas has to be destroyed or removed for diabetes to develop in otherwise healthy individuals.

Several disease processes affecting the pancreas can lead to diabetes, some of which are listed in Table 23.1. Most of these conditions damage the exocrine as well as endocrine components of the pancreas. The exocrine parenchyma and islet tissue lie in intimate contact with each other and are functionally related. This may explain why parenchymal disease can impair β-cell function [2, 3].

Acute pancreatitis

Acute pancreatitis varies considerably in its impact on the gland and its metabolism. Pathological findings vary from mild oedema to haemorrhagic necrosis, and the clinical presentation spans a wide spectrum from mild to fulminating or fatal illness.

The most common causes of acute pancreatitis are alcoholism and gallstone disease. Table 23.2 sets out the causes of acute pancreatitis. It is of interest that diabetes is, in itself, a risk factor for acute pancreatitis, and the use of certain classes of glucose-lowering agents, particularly the glucagon-like peptide-1 receptor agonists and the dipeptidyl peptidase-4 inhibitors, has been reported to be associated with acute pancreatitis [4, 5]. Recent systematic reviews have either failed to confirm a link between the use of these agents and acute pancreatitis or have shown only a minor increase in risk [6]. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) continue to state that the currently available data do not support a causal relationship between incretin-based drugs and pancreatitis [7].

Classically, the disease presents with sudden onset of epigastric pain, associated with nausea and vomiting, aggravated by food and partially relieved by sitting up and leaning forward. Physical examination reveals low-grade fever, tachycardia, and hypotension. Jaundice may also be found infrequently. Cullen sign (periumbilical discoloration) and Grey Turner sign (flank discoloration) indicate severe necrotizing pancreatitis.

Commonly found metabolic abnormalities include hyperglycaemia, hypocalcaemia, hyperlipidaemia, hypoalbuminaemia, and coagulation disorders [8]. Serum levels of amylase and lipase are elevated, but these are neither sensitive nor specific. Computed tomography (CT) or magnetic resonance imaging (MRI) shows oedema of the pancreas. Loss of the normal enhancement on dynamic CT scanning indicates pancreatic necrosis.

Most patients with acute pancreatitis develop transient hyperglycaemia, which mostly results from a rise in glucagon levels rather

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Table 23.1 Pancreatic diseases associated with glucose intolerance and diabetes.

Inflammatory
Acute
Chronic, including fibrocalculous pancreatic diabetes
Infiltration
Hereditary haemochromatosis
Secondary haemochromatosis
Very rare causes: sarcoidosis, amyloidosis, cystinosis
Neoplasia
Adenocarcinoma of the pancreas
Glucagonoma
Surgical resection or trauma
Cystic fibrosis

Table 23.2 Causes of acute pancreatitis.

Common (75% of cases)	Uncommon
Alcohol abuse	**Drugs**
Gallstone disease	Sulfonamides
Idiopathic	Tetracyclines
	Valproate
	Didanosine
	Oestrogens
	Metabolic disorders
	Hypertriglyceridaemia
	Hypercalcaemia
	Diabetic ketoacidosis
	Infections
	Mumps, coxsackie, and HIV viruses
	Mycoplasma pneumoniae
	Trauma
	Abdominal injury
	Surgery, including ERCP
	Miscellaneous
	Hereditary relapsing pancreatitis
	Pancreatic cancer
	Connective tissue diseases
	Pancreas divisum

ERCP, endoscopic retrograde cholangiopancreatography; HIV, human immunodeficiency virus.

than from β-cell injury [9]. Hyperglycaemia is usually mild and resolves within days to weeks without needing insulin treatment. Permanent diabetes is rare and occurs mostly in cases with fulminant disease and multiorgan failure, in which the incidence approaches 25% [10]. Blood glucose levels exceeding 11.1 mmol/l (200 mg/dl) during the first 24 hours indicate a poor prognosis [11]. Following an episode of acute pancreatitis, individuals have a greater than twofold increased risk of developing diabetes over the next five years [12].

Non-specific elevations of serum amylase and lipase may also be found in diabetic ketoacidosis [13]. Acute pancreatitis, however, may affect up to 11% of individuals with ketoacidosis, usually with mild or even no abdominal pain [11].

Chronic pancreatitis

This condition is characterized by progressive and irreversible destruction of the exocrine pancreatic tissue, leading to exocrine pancreatic insufficiency and varying degrees of glucose intolerance, which often require insulin. The causes of chronic pancreatitis vary according to the geographical location (Table 23.3).

Alcohol misuse accounts for most of the cases (>85%) in European and North American populations. Alcohol alters the composition of pancreatic secretions, leading to the formation of proteinaceous plugs that block the ducts and act as foci for calculi formation. Tropical chronic pancreatitis is a distinct form of the disease that is not associated with excessive alcohol intake and is prevalent in low- and middle- income countries [14, 15].

Hereditary chronic relapsing pancreatitis is a rare entity, inherited in an autosomal dominant fashion. Mutations in a number of genes have been implicated, including *PRSS1* (encoding cationic trypsinogen), *SPINK1* (serine protease inhibitor, Kazal type 1), and *CFTR* (cystic fibrosis transmembrane conductance regulator) [16–19].

Obstructive chronic pancreatitis is a rare condition that follows occlusion of pancreatic ducts by tumours, scarring, pseudocysts, or congenital anomalies. Stones are not seen. Surgery or endoscopic dilatation may occasionally be curative.

Idiopathic pancreatitis, which accounts for 10–20% of all cases, affects two distinct age groups, one with onset at 15–25 years and the other at 55–65 years [20]. Cigarette smoking is a risk factor and mutations in specific genes have also been postulated [19, 21, 22].

Epidemiology

Chronic pancreatitis is prevalent worldwide. The incidence varies between 7 and 14 cases per 100 000 population per year, with significant differences between populations and countries. The incidence appears to have increased over time in many parts of the world [23–27]. Tropical chronic pancreatitis is confined to tropical and subtropical regions of the world, with the highest prevalence rates reported in southern India.

Pathological features

The term chronic calcific pancreatitis accurately describes the pathological changes in over 95% of cases of chronic pancreatitis in European and North American countries. The ductal and acinar lumina are filled with proteinaceous plugs that later calcify, forming small stones composed chiefly of calcium carbonate or calcite. Huge stones can occur, but are more characteristic of tropical pancreatitis. The stones are found diffusely throughout the affected organ. Microscopically, there is atrophy of the ductal epithelium and stenosis of the ducts, associated with patchy fibrosis. There may also be foci of necrosis, with infiltration by lymphocytes, plasma cells, and histiocytes [28]. Ultimately, the pancreas shrivels and develops an opaque capsule that may adhere to surrounding organs.

Table 23.3 Causes of chronic pancreatitis.

Common (90% of cases)	Rare
Alcohol abuse	Hereditary relapsing pancreatitis
Idiopathic	Obstructive chronic pancreatitis
Tropical chronic pancreatitis	

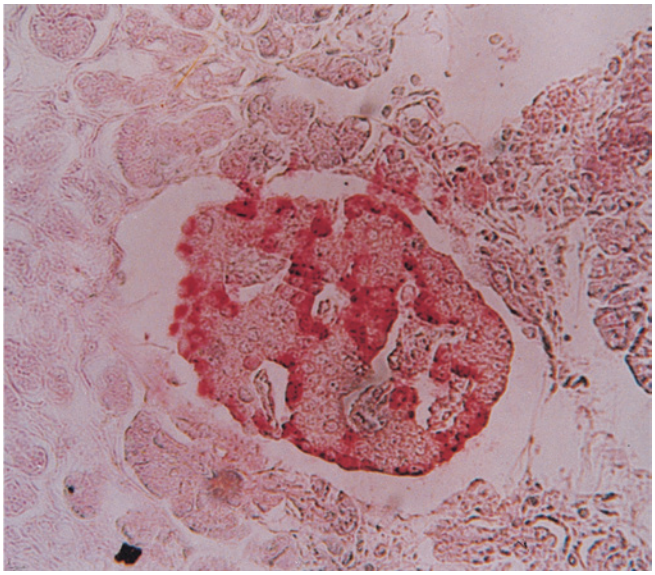


Figure 23.1 Nesidioblastosis, from a case of fibrocalculous pancreatic diabetes, showing islet tissue arising from ductal remnants. Stain aminoethylcarbazole; magnification ×40.

As fibrosis progresses, the acini atrophy and eventually disappear, leaving clusters of islets surrounded by sclerosed parenchyma. Neoformation of islet cells from ductal tissue can occur (nesidioblastosis) (Figure 23.1). Immunohistochemistry studies reveal a generalized decrease in the number of islets, accompanied by overall reduction in β-cell density and insulin immunoreactivity, which correspond to disease duration and C-peptide levels (Figure 23.2; Table 23.4) [30,31].

Clinical features and diagnosis

Abdominal pain is the predominant symptom and the usual reason for seeking medical care. The pain is usually steady, boring, and agonizing, and located in the epigastrium or left hypochondrium with radiation to the dorsal spine or the left shoulder. Bending forward or assuming the knee–chest position relieves the pain. The cause of the pain is unknown, but may relate to increased intrapancreatic or intraductal pressure, or to ischaemia of the pancreas. It tends to remit and relapse and follows an unpredictable course. The development of end-stage pancreatic disease is associated with disappearance of the pain in many cases.

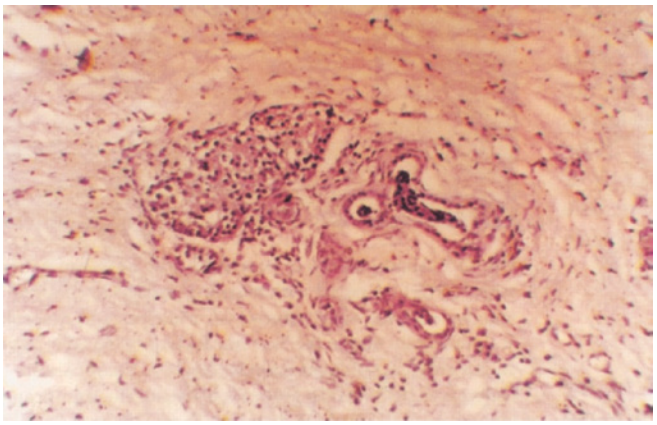
Exocrine pancreatic insufficiency may manifest with steatorrhoea and features of fat-soluble vitamin deficiency, although steatorrhoea may not be apparent on a low-fat diet. The combination of oily and greasy stools with diabetes should raise the suspicion of chronic pancreatitis.

Investigations

Demonstration of pancreatic calculi on a plain X-ray of the abdomen is diagnostic (Figure 23.3). In cases where obvious calculi cannot be found, ultrasonography, CT scanning, or endoscopic retrograde cholangiopancreatography (ERCP) will help to confirm the diagnosis (Figure 23.4). ERCP is considered the gold standard and usually reveals irregular dilatation of the pancreatic ducts with filling defects caused by stones (Figure 23.4a). CT scanning shows patchy increases in parenchymal density and, ultimately, atrophy of the gland.

Exocrine pancreatic function can be assessed by measuring the urinary excretion of compounds that are liberated in the gut by pancreatic enzyme action on orally ingested precursors such as N-benzoyl-L-tyrosyl-p-aminobenzoic acid (NBT-PABA) or fluorescein dilaurate (pancreolauryl). Screening tests of pancreatic enzymes (faecal chymotrypsin, faecal elastase) are also used, as they are simpler to perform but are less specific. Measurement of pancreatic output (via a tube placed in the duodenum) following ingestion of the Lundh test meal may also be helpful. Serum amylase is usually normal, except during acute attacks.

(a)



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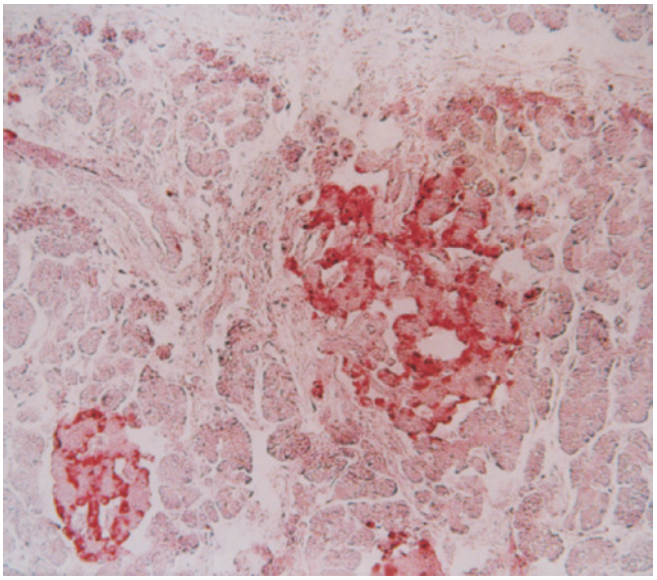


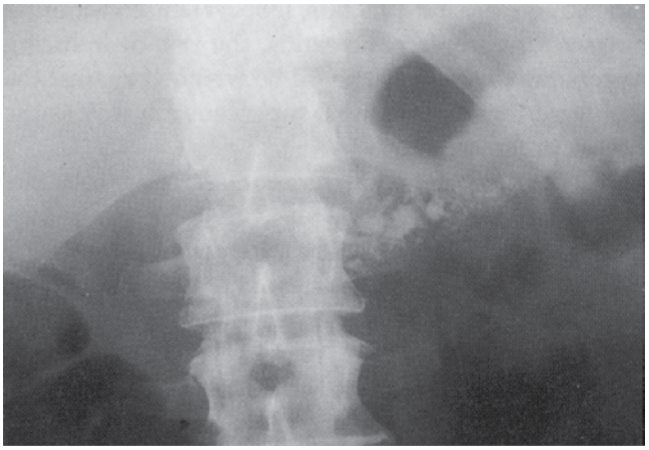
Figure 23.2 Histological features of chronic pancreatitis, from cases of fibrocalculous pancreatic diabetes. (a) Exocrine tissue is entirely replaced by dense fibrosis that spares the islets. Haematoxylin and eosin stain; magnification ×40. (b) A hyperplastic islet. Section immunostained for insulin; magnification ×40.

Table 23.4 Islet cell changes in chronic pancreatitis.

Cell type	Changes observed
β cells	Decreased numbers (40% below normal)
α cells	Increased numbers
β cell : α cell ratio	0.6–2.5 (in normal health 3.0–3.5)
PP cells	Increased numbers
δ cells	Unchanged

Source: Based on Yajnik et al. 1992 [29].

(a)



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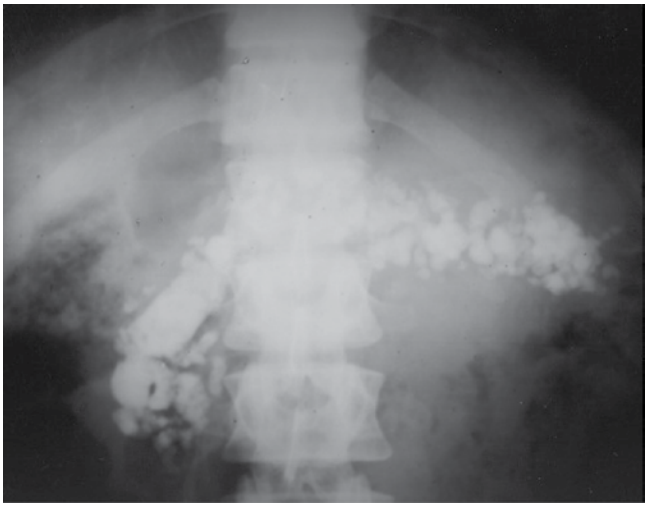
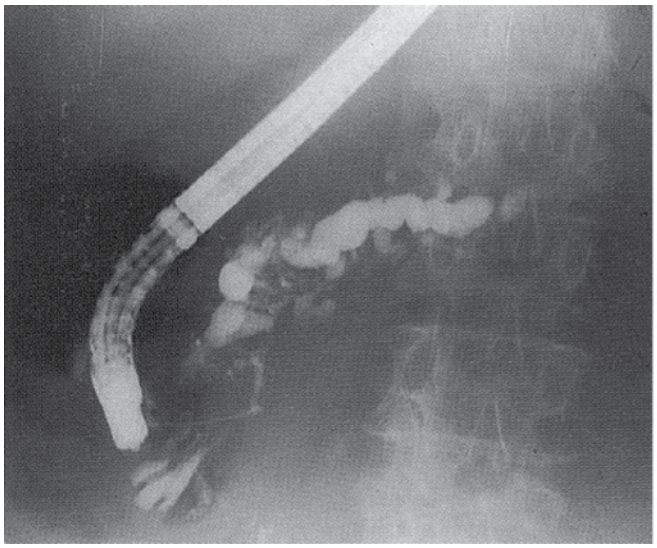


Figure 23.3 Pancreatic calculi, showing characteristic patterns in (a) alcoholic chronic pancreatitis and (b) fibrocalculous pancreatic diabetes.

(a)



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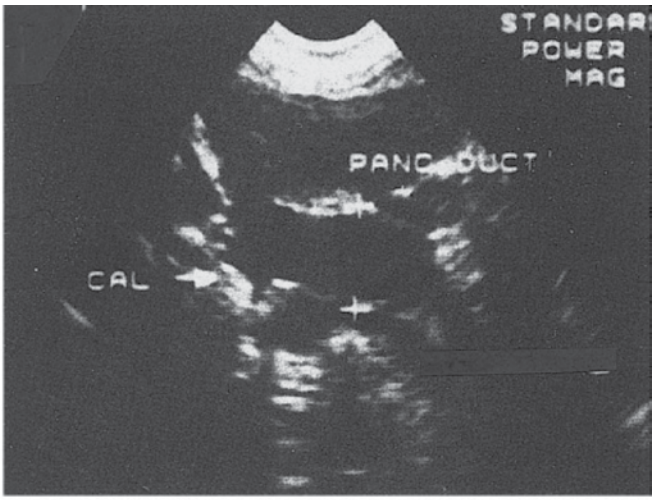

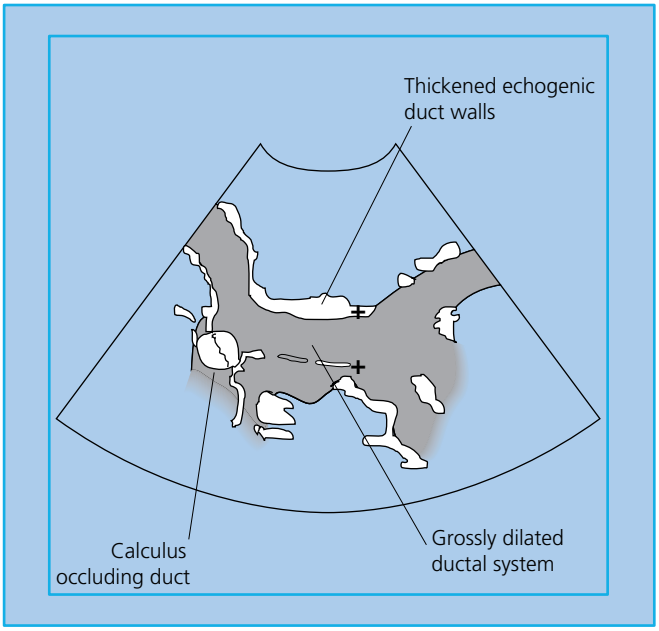

Figure 23.4 Investigations in chronic pancreatitis. (a) Endoscopic retrograde cholangiopancreatogram, showing dilatation and irregularity of the pancreatic ductal system in a person with alcoholic chronic pancreatitis. Source: Courtesy of Professor Jonathan Rhodes, Liverpool, UK. (b) Ultrasound scan of the pancreas from a person with fibrocalculous pancreatic diabetes, demonstrating highly echogenic parenchyma and duct walls (fibrosis), grossly dilated ducts, and calculi. The lower drawing shows the salient features of the ultrasound scan. Source: Courtesy of Dr S. Suresh, Chennai, India.

Diabetes in chronic pancreatitis

Abnormal glucose tolerance and diabetes complicate around 40–50% of cases of chronic pancreatitis. Unlike acute pancreatitis, the cause here is damage to the β cells, owing to loss of trophic signals from the exocrine tissue [2,32], although some authors have postulated a role for reduced insulin sensitivity as well [33]. The diabetes is of insidious onset and usually occurs several years after the onset of pain. The prevalence has been assessed at 60% after 20 years [34]. Half or more of patients require insulin for optimal glycaemic management [35,36], but ketoacidosis is rare, even if insulin is withdrawn. Possible explanations include better preservation of β-cell function (compared with type 1 diabetes) [37], reduced glucagon secretion, and lower body stores of triglyceride, the major substrate for ketogenesis [29,37]. On account of the lower glucagon reserve, these people are also prone to severe and prolonged hypoglycaemia, and often diabetes is difficult to manage with wide fluctuations of blood glucose levels.

Chronic diabetic complications

It was originally thought that people with pancreatic diabetes were not at increased risk of microvascular complications; however, retinopathy [38] and nephropathy [39] occur at frequencies similar to those with type 2 diabetes, while the prevalence of neuropathy might be higher [40,41]. The risks of macrovascular complications, nevertheless, are relatively low. This may partly be explained by the favourable blood lipid profile that often accompanies the malnutrition commonly seen in these people [42].

Management of diabetes in chronic pancreatitis

Removal of obvious causes, such as alcohol and hypertriglyceridaemia, will help to prevent progression of the damage to the gland. Pain can be very difficult to manage. Measures include total abstinence from alcohol, dietary modification (small frequent meals with low fat content), analgesics, and the somatostatin analogue octreotide, which suppresses pancreatic exocrine secretion. In a subgroup of individuals, massive doses of non-enteric-coated preparations of pancreatic enzymes may reduce pain. Surgical interventions include sphincterotomy, internal drainage of pancreatic cysts, endoscopic removal of calculi (via ERCP), insertion of duct stents, and denervation procedures. Total resection of the pancreas followed by whole pancreas or islet cell transplantation is an option for intractable cases. Malabsorption can be effectively treated with a low-fat diet with pancreatic enzyme supplements (along with histamine H_2 blocker or proton pump inhibitor to block gastric acid secretion) taken at meal times.

Diabetes should be managed along conventional lines, with a few caveats. High carbohydrate and protein intakes are encouraged along with fat restriction in order to prevent steatorrhoea while preventing weight loss. Over 80% of these individuals require insulin; however, the required doses are typically low, around 30–40 units/day [35,36]. Despite this, frequent and severe hypoglycaemia may occur as a result of reduced glucagon secretion.

Individuals with type 2 diabetes exhibit evidence of reduced exocrine pancreatic function, albeit not to the degree found in 'pancreatic' diabetes. In a study from India, the prevalence of exocrine pancreatic insufficiency (measured by the faecal chymotrypsin assay) was 4.5% in type 2 diabetes, as compared to 88% and 24% in fibrocalculous pancreatic diabetes and type 1 diabetes, respectively [43]. Pancreatic insufficiency has been postulated to occur due to loss of the trophic action of insulin on the exocrine tissue; however, autonomic neuropathy affecting the enteropancreatic reflexes may play a role in the pathogenesis [44]. Routine screening of persons with type 2 diabetes for exocrine pancreatic insufficiency in the absence of symptoms is not recommended.

Tropical chronic pancreatitis

This is a distinct variety of chronic pancreatitis seen predominantly in low- and middle-income countries in the tropical and subtropical regions of the world [45,46]. This entity was first reported in 1959 by Zuidema [46] in people from Indonesia, but the disease was subsequently reported in several countries in Africa and Asia. The highest prevalence appears to be in southern India, particularly in the states of Kerala and Tamil Nadu [47]; however, the prevalence seems to be declining even in these areas.

The disease usually starts in childhood with recurrent abdominal pain and during adolescence progresses to large pancreatic calculi and ductal dilatation (Figures 23.3 and 23.5). By adulthood, frank diabetes is found in more than 90% of these individuals [48]. Nevertheless, it remains a rare cause of diabetes, constituting less than 1% of all cases of diabetes (and a slightly higher proportion of all young-onset diabetes) even in regions where it is most prevalent [49,50]. A recent population-based study in urban southern India reported a prevalence of 0.36% among people with self-reported diabetes and 0.019% among the general population [51].

The term tropical chronic pancreatitis is used to denote the prediabetes stage of the disease, whereas the term fibrocalculous pancreatic diabetes is used to describe the clinical picture once diabetes has supervened (Figure 23.6).

Figure 23.5 Calcite stones of various sizes removed from the pancreas of a person with fibrocalculous pancreatic diabetes.

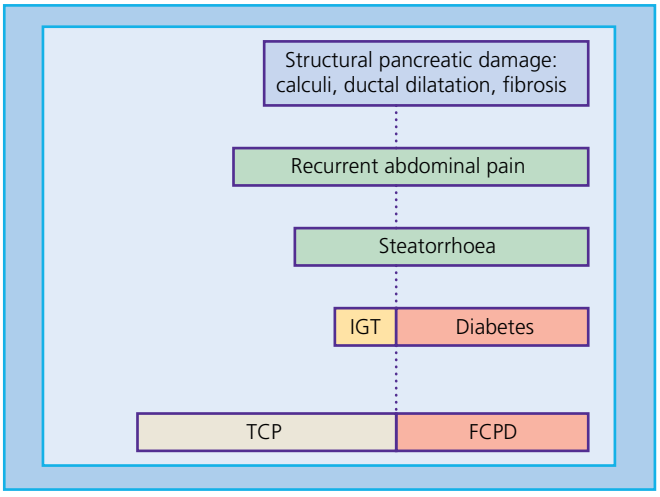

Figure 23.6 Natural history of tropical calcific pancreatitis (TCP) and fibrocalculous pancreatic diabetes (FCPD). IGT, impaired glucose tolerance.

The aetiology of the condition remains unknown. Poor nutrition has been implicated as a possible factor; however, this may be a consequence rather than a cause of the pancreatopathy. The condition may also affect well-nourished individuals [52]. In the past, attention was focused on the role of dietary toxins such as cyanogens (found in cassava), but this link has not been substantiated. Cases tend to cluster in families, which may suggest a genetic aetiology for the disease [53–56]. Several studies have reported an association of tropical chronic pancreatitis with the *SPINK1* gene [57–63], as also with the cathepsin B (*CTSB*) gene [64, 65]. A role has been suggested for oxidant stress and free radical–mediated injury, but this has not been proven conclusively [66].

Salient differences between alcoholic chronic pancreatitis and tropical chronic pancreatitis are summarized in Table 23.5. The classic clinical triad of tropical chronic pancreatitis comprises abdominal pain, steatorrhoea, and eventually diabetes. The disease often progresses steadily from euglycaemia through impaired glucose tolerance to frank diabetes. Most people require insulin but are generally not prone to ketosis; some can be managed with oral anti-diabetes agents (Figure 23.7). The risk of developing pancreatic carcinoma in tropical chronic pancreatitis is 100-fold greater than in those without the disease and is much higher than in other forms of chronic pancreatitis [67]. Pancreatic malignancy should be suspected in individuals with tropical chronic pancreatitis if they complain of intractable pain or significant weight loss even after attaining optimal glycaemic levels. Management of tropical chronic pancreatitis and fibrocalculous pancreatic diabetes is similar to that outlined for chronic pancreatitis.

Table 23.5 Differences between tropical chronic pancreatitis and alcoholic chronic pancreatitis.

	Tropical chronic pancreatitis	Alcoholic chronic pancreatitis
Demographic features		
Male : female	70 : 30	90 : 10
Peak age at onset (years)	20–30	30–50
Socioeconomic status	Poor > affluent	All groups
Alcohol abuse	Absent	Present
Pancreatic morphology		
Prevalence of calculi	>90%	50–60%
Features of calculi	Large; in large ducts	Small, speckled; in small ducts
Ductal dilatation	Usually marked	Usually moderate
Fibrosis	Heavy	Variable
Risk of pancreatic cancer	Markedly increased	Increased
Diabetes		
Prevalence	>90%	50%
Time course	Faster evolution	Slower evolution

Hereditary haemochromatosis

This condition, also called idiopathic or primary haemochromatosis, is the most common autosomal recessive genetic disorder in people of northern European ancestry, with a prevalence of 4–5 per 1000 [68, 69]. The classic triad of diabetes, cirrhosis, and bronzed hyperpigmentation of the skin was first described by Trousseau in 1865 and called 'haemochromatosis' by von Recklinghausen in 1889 [70].

Aetiology and pathology

Genetic basis

Most cases of primary haemochromatosis arise from mutations in the haemochromatosis gene (*HFE*), located on the short arm of chromosome 6, close to the major histocompatibility complex (MHC), which explains the linkage with human leucocyte antigen (HLA) A3 [71]. The HFE protein encoded by this gene is expressed on the cell surface of various tissues, including the enterocytes of the duodenal brush border, where iron is chiefly absorbed. The *HFE* gene modulates iron absorption by binding to the transferrin receptor. In two-thirds of cases, a C282Y mutation (substitution of cysteine by tyrosine at position 282) in the *HFE* gene is responsible [68]. Another mutation, H63D, seems to act synergistically with C282Y [72]. These mutations inhibit the binding of HFE to transferrin, leading to an excessive and inappropriate increase in intestinal iron absorption and greatly increased body iron stores. Non-*HFE* mutations are also rarely found to be responsible in some cases.

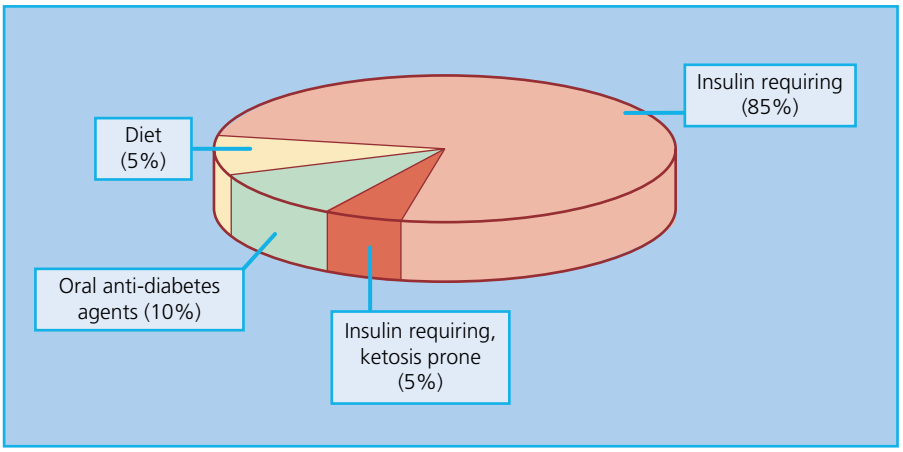

Figure 23.7 The spectrum of diabetes in fibrocalculous pancreatic diabetes. Source: Data from Mohan et al. 1989 [42].

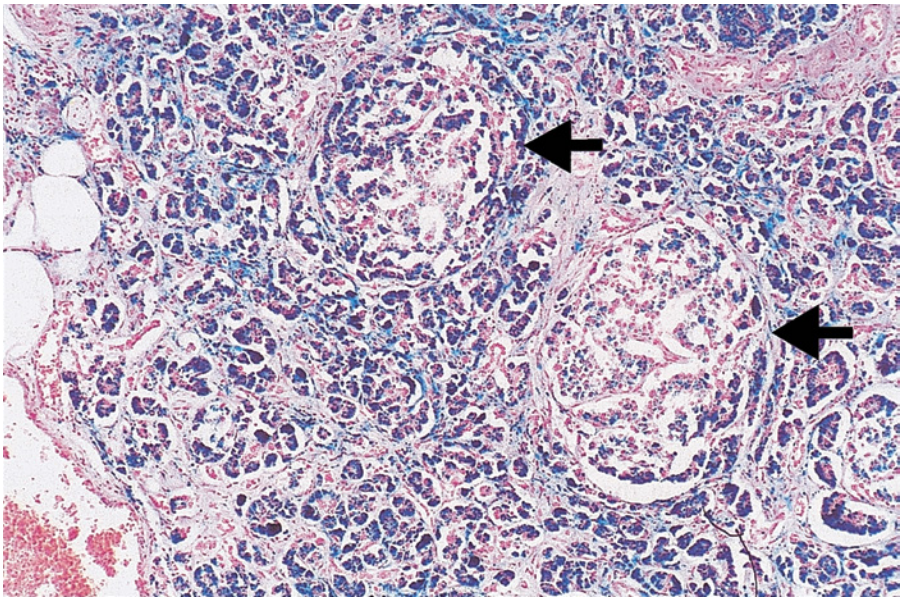

Figure 23.8 Hereditary haemochromatosis. Perls stain shows heavy iron deposition (blue) in exocrine and islet tissue in the pancreas (arrows). Original magnification ×375. Source: Courtesy of Dr A. Clark, Wirral Hospital, UK.

Pathophysiology

The primary defect is excessive iron absorption across the mucosa of the proximal small intestine, which continues even in the setting of greatly increased total body iron stores (often 15–20 g; cf. normal adult iron stores of 1–2 g). Excess iron is deposited preferentially in the liver, pancreas (exocrine tissue as well as islets), pituitary, heart, and parathyroids (Figure 23.8). Tissue injury is postulated to occur as a result of rupture of iron-laden lysosomes, generation of free radicals (by decomposition of hydrogen peroxide catalysed by the ferrous and ferric ions – the Fenton reaction), and the stimulation of collagen synthesis by activated stellate cells.

Clinical features

The classic clinical features are hepatic cirrhosis, diabetes, and skin hyperpigmentation ('bronzed diabetes') (Figure 23.9). Hepatic fibrosis and cirrhosis usually only develop in those aged over 40 years, unless other factors such as alcoholism are present. Portal hypertension, hepatic failure, and hepatocellular carcinoma (in 15% of cases) are late sequelae [73]. Bronzing of the skin, which occurs in 70% of cases but may be less evident in darker-skinned races, is caused by both iron deposition in the subcutaneous tissue and increased melanin in the basal dermis. Hypopituitarism, hypogonadism, hypoparathyroidism, and chondrocalcinosis with pseudogout are less common features.

Presenting symptoms include weakness, weight loss, diabetes symptoms, arthralgia, erectile dysfunction, and skin pigmentation. Signs include hepatosplenomegaly, heart failure, skin pigmentation, testicular atrophy, arthropathy, hypogonadism, and occasionally hypothyroidism. Many people with haemochromatosis, however, are asymptomatic and may be detected during investigation for unrelated reasons or through genetic screening of family members of those with haemochromatosis.

Diabetes in primary haemochromatosis

The prevalence of diabetes depends on the severity of iron overload and presence of cirrhosis [74]. Up to 50% of these individuals have glucose intolerance and 25% have overt diabetes [75], although the disease is an extremely rare cause of diabetes in the

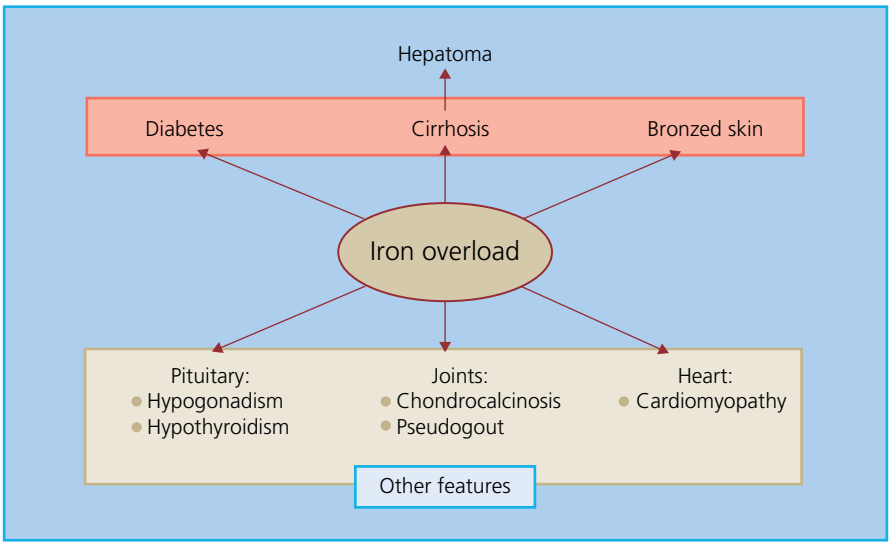

Figure 23.9 Clinical features of hereditary haemochromatosis. The classic triad comprises diabetes, cirrhosis, and hyperpigmentation of the skin ('bronzed diabetes').

general population. The prevalence is steadily declining as the diagnosis is being made earlier, before significant pancreatic damage has occurred. Both insulin resistance and β-cell failure contribute to the development of diabetes, and most individuals eventually require insulin. These individuals are prone to both microvascular and macrovascular complications [73], the risk of nephropathy being particularly high in those carrying the H63D mutation [76].

Investigations and diagnosis

The diagnosis should be suspected in any person with diabetes, hepatomegaly or liver disease, skin pigmentation, arthritis, and hypogonadism. A high index of suspicion is required to make an early diagnosis, because significant iron overload can exist with few or none of these clinical manifestations.

The total-body iron stores can be assessed using measurement of serum ferritin and percent saturation of transferrin. Serum ferritin is a useful screening test for relatives of affected individuals, but because ferritin is an acute-phase reactant, the levels of which can be elevated in inflammatory states, abnormally high results should be confirmed by other tests (Table 23.6) [77]. Serum iron and percentage saturation of transferrin are elevated early in the course of the disease, but lack specificity. A combined measurement of the percentage transferrin saturation and serum ferritin levels provides a simple and reliable screening test for hemochromatosis. A positive test mandates genetic testing.

The role of liver biopsy in the diagnosis and management of haemochromatosis has significantly diminished following the development of genetic testing for the C282Y mutation. The major role of liver biopsy at the present time is to exclude the presence of cirrhosis, which is a major risk factor in the development of hepatocellular carcinoma. Hepatic iron overload can also be detected using imaging techniques such as CT scanning or MRI.

All first-degree adult relatives of individuals with haemochromatosis should be tested for C282Y and H63D mutations in an attempt to detect disease in the early pre-cirrhotic phase, at which stage treatment can prevent further progression.

Treatment

Treatment of hereditary haemochromatosis is by repeated venesection, which must be started as early as possible. Removal of excess iron by venesection prevents diabetes and cirrhosis and prolongs survival [74]. Chelating agents such as desferrioxamine and deferasirox are more expensive, less safe, and less effective than venesection. Diabetes may be improved by venesection, but usually requires insulin treatment. Management is often complicated by hypoglycaemia caused by concomitant α-cell damage and glucagon deficiency. Hepatic transplantation for hereditary haemochromatosis was previously associated with a poor prognosis, but survival rates have improved of late. Diabetes tends to worsen after transplantation because of the use of immunosuppressant drugs [78]. Hepatocellular carcinoma is a late complication and may be an indication for transplantation if the disease remains localized.

Table 23.6 Diagnostic tests in hereditary haemochromatosis.

	Haemochromatosis	Normal
Serum iron (μg/dl)	180–300	50–150
Transferrin saturation	80–100	20–50
Total iron-binding capacity (μg/dl)	200–300	250–370
Serum ferritin (μg/dl)		
Men	500–6000	20–300
Women	500–6000	15–250
Hepatic iron concentration (μg/g dry weight)	10 000–30 000	300–100

1 μg/dl of serum = 5.6 μmol/l. The calculated total iron binding capacity in μg/dl is converted to μmol/l by multiplying by 0.1791.
Source: Based on Fried Hagedorn 2000 [77].

Secondary haemochromatosis

Iron overload can also occur as a consequence of repeated blood transfusion and disorders of erythropoiesis such as thalassemia and sickle cell anaemia, in which case the condition is termed secondary haemochromatosis or hemosiderosis. Pancreatic damage and diabetes frequently result. The duration of disease and number of transfusions correlate well with the degree of glucose intolerance. Iron overload may induce autoimmune attack against the β cells, thereby contributing to the development of diabetes [79].

Pancreatic neoplasia

Adenocarcinoma of the pancreas is the fifth most common cause of cancer death and is increasing in its incidence [80]. It has a poor prognosis, with a five-year survival rate of less than 3%. Although diabetes has long been associated with pancreatic adenocarcinoma, the nature and strength of the association remain controversial. A meta-analysis of 20 epidemiological studies showed a twofold increased risk of pancreatic cancer among people with diabetes of more than five years' duration [81], suggesting that diabetes is a risk factor for the neoplasm. Other studies, however, have concluded that the cancer preceded and caused the diabetes [82], a view supported by observations that diabetes may improve after resection of the tumour. Some studies have even suggested that diabetes protects against pancreatic cancer [83]. Tropical chronic pancreatitis is associated with a 100-fold increase in the risk of developing pancreatic carcinoma [65]. Currently available data do not support an association between the use of incretin-based therapies for diabetes and the risk of pancreatic carcinoma [7, 84, 85].

The diagnosis of pancreatic carcinoma should be suspected in any person with type 2 diabetes who complains of unexplained weight loss (despite insulin therapy and apparently good glucose levels), back pain, or jaundice.

Pancreatic surgery and diabetes

Diabetes is a frequent complication of pancreatic resection performed for various indications. The incidence and severity of diabetes depend on the extent of resection of the distal segment, where the islets are most abundant. In one study, diabetes developed in 56% of cases following distal resection [86]. Diabetes is more likely to follow subtotal pancreatectomy than procedures such as lateral pancreaticojejunostomy and pancreaticoduodenectomy (Whipple procedure). Diabetes is obviously inevitable following total pancreatectomy.

Management of diabetes caused by pancreatic surgery

The diabetes is usually difficult to manage, with wide excursions in blood glucose levels. Individuals are exquisitely insulin sensitive and prone to hypoglycaemia as a result of the loss of glucagon function. Frequent small meals and multiple small doses of insulin can minimize these problems to an extent. Use of a subcutaneous insulin infusion pump may be beneficial in some cases. People with diabetes following pancreatectomy are ideal candidates for whole pancreas or islet cell transplantation. Any associated exocrine pancreatic insufficiency should also be addressed. Meals should be low in fat and high in carbohydrate and protein. Pancreatic enzyme therapy will help in controlling steatorrhoea and stabilizing blood glucose [87].

Cystic fibrosis

Cystic fibrosis is a multisystem disease characterized by recurrent airway infection leading to bronchiectasis, pancreatic insufficiency, abnormal sweat gland function, and urogenital dysfunction. It is an autosomal recessive disorder caused by mutations in the *CFTR* gene located on chromosome 7q22. This gene encodes a protein, CFTR, which regulates the chloride secretion across epithelial surfaces. Various mutations have been described, of which deletion of the phenylalanine residue at position 508 (Δ508) is the most common [88]. The defect produces unusually viscid secretions that lead to pancreatic ductular obstruction, dilatation, and pancreatic insufficiency. The incidence is 1 in 2500 live births in populations of white northern European ancestry, but the disease is much less common in Africans and Asians [89].

The most common clinical features are steatorrhoea, failure to thrive and growth retardation, recurrent lung infections, hepatobiliary complications, osteoporosis, and symptoms of fat-soluble vitamin deficiency such as night blindness. The diagnosis is confirmed by the presence of an elevated sweat chloride concentration in excess of 60 mmol/l.

Diabetes in cystic fibrosis

The incidence of diabetes in children with cystic fibrosis is 2–3% (about 20 times higher than in the general population). The incidence rises steadily through adolescence, with up to 25% of individuals in their 20s developing diabetes and a further 50% having glucose intolerance [90]. Up to 50% of adults develop diabetes by the age of 35–40 years. Occasionally, diabetes is the first manifestation of cystic fibrosis. As the treatment of the lung disease in cystic fibrosis has improved, more and more people are surviving into adulthood, leading to an increase in the prevalence of cystic fibrosis diabetes.

The major factor in the pathogenesis of diabetes is damage to the pancreatic β cells secondary to exocrine pancreatic degeneration. There is a progressive decrease in insulin secretion with increasing age, and a decrease in the number of β cells associated with inflammation, fibrosis, and amyloidosis of the pancreas. There may also be a direct effect of the cystic fibrosis mutation on insulin secretion, as the CFTR has a role in β-cell function and insulin secretion. Other postulated mechanisms include enhanced absorption of glucose [91], lowered chloride levels within the β cell leading to reduced glucose responsiveness [92], and autoimmune attack against the β cell, which may explain why type 1 diabetes is more common in relatives of people with cystic fibrosis [93]. The physiological insulin resistance of normal puberty may also contribute. Interestingly, diabetes develops more commonly in people homozygous for Δ508 than in heterozygotes [94].

Diabetes is usually insidious in onset and characterized by a delayed, flattened, and prolonged insulin secretory response to glucose [95]. Insulin secretion in people with cystic fibrosis declines from childhood, even in those with normal glucose levels. Insulin sensitivity is usually normal, but reduced insulin sensitivity contributes to hyperglycaemia in situations where there is another cause of insulin resistance, such as infection or systemic corticosteroid treatment. Basal insulin secretion is relatively preserved, but the insulin response to a glucose load is reduced and delayed. Consequently, fasting blood glucose levels are normal initially and the individual may only have intermittent elevations of post-prandial glucose to begin with. There is a characteristic pattern of abnormal glucose levels, with glucose levels being lowest before breakfast and rising after meals, with the highest levels in the evening. In time, post-prandial hyperglycaemia becomes established and fasting glucose levels subsequently rise to levels diagnostic of diabetes [96]. Ketoacidosis is rare, although insulin treatment is usually required.

As persons with cystic fibrosis diabetes now survive longer [88], chronic microvascular complications are also frequently seen, although macrovascular disease is virtually unknown. The major impact of cystic fibrosis diabetes, however, is on lung function and mortality. Studies dating back to the 1980s demonstrated significant increases in mortality in those with cystic fibrosis diabetes even after adjustment for other risk factors. Health appears to start to deteriorate two to six years prior to a diagnosis of diabetes, with decreases in weight, body mass index, and markers of lung function up to six years prior to the diagnosis of diabetes. The reasons why worsening glycaemia adversely affects clinical status are not fully understood, but are likely to be multifactorial and include the gradual loss of the anabolic effect of insulin and elevated airway glucose levels that may promote bacterial growth.

Management

The International Society for Paediatric and Adolescent Diabetes (ISPAD) and the American Diabetes Association (ADA) recommend that all children with cystic fibrosis be screened annually for diabetes with an oral glucose tolerance test, starting from 10 years of age [96, 97]. Currently the diagnostic criteria are the same as for other forms of diabetes, but there have been calls to lower the thresholds to recognize that levels of glycaemia that are below the standard thresholds may still be associated with worsening lung function and weight loss. The oral glucose tolerance test is the diagnostic test of choice, but this should not be performed during acute exacerbations of pulmonary disease, particularly if the treatment includes glucocorticoids. There is some evidence that glycated haemoglobin (HbA_{1c}) may be useful for diagnosing cystic fibrosis diabetes, although this is not currently recommended. The utility of continuous glucose monitoring is being assessed. Although some people initially respond to sulfonylureas, most ultimately need insulin and this is reflected in most guidelines for treatment, which recommend insulin as the treatment of choice [98]. In addition to managing diabetes, insulin may also improve body weight and pulmonary and pancreatic function [90, 99, 100]. Early diagnosis and treatment of cystic fibrosis diabetes may help to preserve lung function [101]. Annual monitoring for complications of diabetes is recommended, starting five years after the diagnosis of diabetes [97].

Dietary modification in people with cystic fibrosis who also have diabetes presents much the same difficulties as in people with chronic pancreatitis. A diet rich in carbohydrates and protein but restricted in fat is recommended. Oral pancreatic enzyme therapy helps to improve nutrient digestion and absorption. Enteric-coated preparations of lipase can control steatorrhoea. Fibrosing colonopathy is a concern in individuals receiving higher strengths of lipase [102].

Conclusion

Although rare, diabetes secondary to pancreatic disease is potentially important. The underlying pancreatic disease may need treatment in its own right, while disorders with a genetic basis must be identified so that other family members can be screened. Diagnosis of pancreatic diabetes requires a high index of suspicion. Suggestive symptoms include features of pancreatic disease (steatorrhoea, unexplained weight loss, or back pain) and severe diabetes, which is difficult to manage, in the absence of a family history of diabetes.

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24 Clinical Presentations of Diabetes

Ee Lin Lim[1] and Roy Taylor[2]

[1] Royal Preston Hospital, Preston, UK

[2] Diabetes Research Group, Institute of Translational and Clinical Research, Newcastle University, Newcastle upon Tyne, UK

Key points

- The classic symptoms of diabetes are thirst, polydipsia and polyuria, weight loss, and tiredness.
- People with type 1 diabetes usually present with classic symptoms and occasionally diabetic ketoacidosis.
- People with type 2 diabetes may present with classic symptoms or the presentation may be asymptomatic and discovered on routine examination or laboratory test.
- Type 2 diabetes may present with complications of diabetes that may be either microvascular or macrovascular.
- Initial diagnosis of type 2 diabetes during acute myocardial infarction or stroke is common.
- The mode of presentation may help distinguish the type of diabetes.
- With advancing age, the renal threshold for glucose increases and thirst perception diminishes.
- Consideration of the impact of the initial consultation on the individual is important.
- Diabetes of onset in pregnancy is important and ideally detected by an effective screening programme.

Diabetes has long since taken over from syphilis as the great imitator, and nowhere is this more apparent than in the wide variation of possible modes of initial presentation. The classic triad of thirst, polydipsia, and polyuria accounts for only a modest proportion of new diagnoses of diabetes. The relatively acute onset of such symptoms associated with loss of weight is the hallmark of type 1 diabetes with ketoacidosis at the extreme. Hyperosmolar hyperglycaemic syndrome (HHS) may precipitate a dramatic presentation of type 2 diabetes to emergency services. Non-specific symptoms including tiredness, general malaise, and repeated or persistent skin infections may lead to a biochemical diagnosis of diabetes. Screening of at-risk groups or individuals allows early diagnosis. Regrettably, the nature of the condition is such as to allow it to remain asymptomatic for years, allowing the clinical presentation to be a long-term complication of diabetes. This could be in the form of macrovascular disease (myocardial infarction, stroke, black toe) or in the form of microvascular disease (loss of visual acuity, nephropathy, neuropathy). Pregnancy may cause gestational diabetes mellitus (GDM) that, although it may remit after delivery, does indicate a high risk for future type 2 diabetes.

Clinical considerations at presentation

At the heart of any consultation involving the presentation of diabetes there is a patient. Depending on prior knowledge, *diabetes* may be associated in their mind with blindness and amputation, disability, and premature death. Alternatively, it may be associated with vague concepts of malaise. The individual's beliefs and thoughts on diabetes need to be established if the diagnostic consultation is to be therapeutic. In an era of medicine by numbers, often traduced as *evidence-based medicine*, it is easy to overlook the impact of the consultation itself on the person who will live with diabetes. 'Where were you when the Twin Towers fell?' – 'What was it like when you were told you have diabetes?' The moment is likely to be memorable and influential.

The therapeutic consultation will involve listening, a process that need not be unduly time consuming. 'Do you know of anyone with diabetes? What do you know of diabetes just now?' The information received will allow the person's likely type of diabetes and immediate prognosis to be put into perspective. Together with other aspects of sound clinical history taking, it will also transform that person's view of the consultation. Individuals with diabetes rate *listening* as the most valued attribute of a doctor. Although others may listen too, this cannot be delegated.

At what stage of diabetes is the person in front of you? The implications for the person who was identified on routine screening are quite different from those of someone presenting with a black toe. The former is likely to be at an early stage of a long process with a good chance of modifying disease progression, whereas the latter is likely to have other established tissue complications. Clearly, genetic susceptibility to develop complications plays a part as well as natural history time course. The former individual may never develop more than microaneurysms in the eye and be resistant to diabetic nephropathy. Even if they are to be susceptible to complications, these are amenable to intervention over a period of many years. The latter individual, however, requires clear explanation of what can be done and how future trouble can be avoided. Hippocrates summed it up nicely: 'Cure sometimes, relieve often, comfort always.'

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The possibility of cure should not be overlooked. Diabetes has long been regarded as incurable, but this is not so. Recent advances in our understanding of type 2 diabetes reveal that it is a simple condition of accumulating more fat than can be tolerated by the individual. Durable remission of short-duration type 2 diabetes by substantial and sustained weight loss is possible for those who have the determination and ability to change long-standing behaviour patterns [1]. For such people, this knowledge is life changing and normoglycaemia continues as long as weight regain is avoided [2]. Only 50% of individuals with diabetes of duration longer than eight years can reverse their diabetes, compared with around 90% of those with diabetes for less than four years [3]. Bariatric surgery produces dramatic and long-term cure of type 2 diabetes in the early years of the condition by enforced calorie restriction [4, 5]. However, can the remission results be translated to the diabetes population in the community and is the delivery of such significant weight loss feasible? The Diabetes Remissions Clinical Trial (DiRECT) showed that more than a third of people with type 2 diabetes who took part in a weight management programme delivered through primary care surgeries in England and Scotland remained in remission of their diabetes two years later [6]. Weight loss led to reduced levels of intra-pancreatic fat, which in turn was associated with the recovery of pancreas function and insulin production [7].

Rare causes of diabetes should not be overlooked. Look out for the slatey grey person with large liver and haemoglobin level of 190 g/l. Haemochromatosis is rare as a cause of diabetes, but it is treatable and therefore important (Chapter 23). The hyperglycaemia of a person taking a combination of thiazide diuretic and β-blocker may be ameliorated by use of alternative agents (see Chapter 21). Cushing syndrome may include curable diabetes (Chapter 22). Few people taking systemic steroid therapy can stop treatment just because of the development of diabetes, but diabetes will go away or become much easier to manage when the steroid course finishes.

Types of diabetes

The classification of diabetes has attracted much debate, although most people follow well-defined clinical courses. Currently, those people who appear to have primary, major β-cell failure are classified as having type 1 diabetes. Type 1 diabetes does not present clinically until 80–90% of the β cells have been destroyed. As type 2 diabetes is caused by fat accumulation in liver and pancreas that exceeds a personal threshold [8, 9] and removal of this by substantial weight loss will restore long-term normoglycaemia if done within six years of diagnosis [6, 7], any doubt about type 2 diabetes having a single weight-related aetiology has been removed. Typically, type 2 diabetes presents beyond the age of 30 years in those with an elevated body mass index (BMI). Around 1 in 10 people with newly diagnosed type 2 diabetes have a BMI in the normal range but have gained weight during adult life. The younger the age of onset, the greater is the weight at presentation. The monogenic causes of diabetes are capable of precise genetic description and are clearly separate (Chapter 20). Similarly, pancreatic disease such as chronic pancreatitis, pancreatic carcinoma, and haemochromatosis is capable of precise diagnosis (Chapter 23). Type 2 diabetes, however, is often used to cover conditions that do not fit into the other, more easily defined categories. More subtypes will be identified in due course (Chapter 2).

The important practical question at the initial presentation is whether insulin therapy is necessary. In some circumstances there is no doubt, such as diabetic ketoacidosis (DKA) or severe weight loss with ketonuria and glycosuria in a child (Figure 24.1). More usually in adult practice, the question must be carefully considered. Table 24.1 lays out the common and distinguishing features from the clinical history, examination, and urinalysis to help the clinician come to the answer. The subsequent sections consider the separate features in context.

Thirst, polydipsia, and polyuria

These symptoms result from an osmotic diuresis caused by hyperglycaemia. The symptoms are common to all types of diabetes, although the time course is likely to be shorter and the symptoms more severe in type 1 diabetes. Not infrequently, sugar-containing carbonated drinks are selected to slake thirst, leading to worsening of symptoms. A careful history documenting the time course of symptoms and any change in intake of specific drinks is important. Remembering how many times per day urine is passed is not easy, but nocturia is more clear-cut and the number of times urine is passed at night should be quantified. 'Do you need to drink water when you get up at night?' is a reasonably objective measure of thirst.

For glucose to escape into the urine, plasma glucose concentration must exceed the renal threshold for tubular reabsorption of glucose and the absolute amount of glucose delivered to the renal tubules must exceed the maximum absorptive capacity. The renal threshold averages 11 mmol/l, but displays a wide individual variation of around 6–14 mmol/l [10]. Additionally, the maximum absorptive capacity varies with age, such that older people exhibit glycosuria at higher plasma glucose levels [11].

The rise in maximum renal tubular absorptive capacity with increasing age is clinically significant, as older people will only develop osmotic symptoms at higher plasma glucose levels. Conversely, a negative urine test is even less likely to exclude a diagnosis of diabetes than in younger people. In addition to the need for higher plasma glucose levels in older people to produce osmotic symptoms, the threshold for triggering the sensation of thirst rises with advancing years [12]. This is important because, once the maximum renal absorptive capacity has been exceeded, dehydration will become considerably more advanced before thirst is sensed. These age-related changes are highly relevant to the development of severe hyperosmolar states.

The presence of chronic hyperglycaemia itself changes the renal sensitivity to vasopressin such that thirst is not appreciated despite rising plasma osmolarity [13]. Hence, the combination of undiagnosed diabetes and advanced age is particularly potent in delaying appropriate action to increase oral fluid intake as dehydration progresses. The clinical features identified from the history at presentation will vary in relation to the factors mentioned. In older people, thirst may not be experienced despite an osmotic diuresis and polydipsia will be absent. The most reliably quantitated feature of an osmotic presentation is therefore frequency of nocturia, and specifically an increase from habitual levels.

In children, enuresis may be the first symptom of polyuria. Sudden onset of enuresis should always prompt testing of urine for glucose. A urine test is entirely appropriate as an initial screen in this situation, as the absence of glucose from the urine absolutely excludes hyperglycaemia as a potential cause of polyuria.

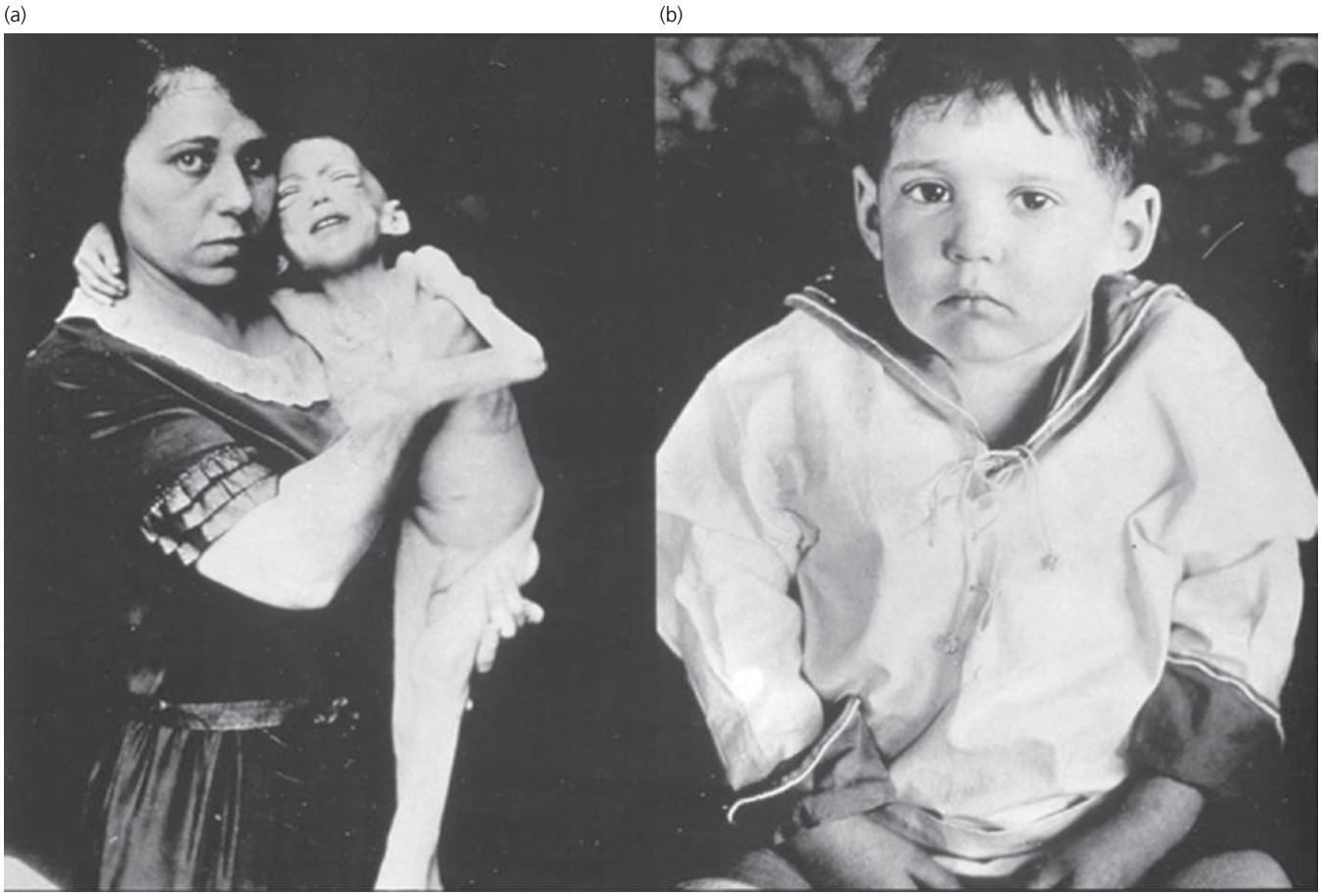

Figure 24.1 A 3-year-old boy before and after three months of insulin therapy (1922). (a) The severe wasting of muscle and adipose tissue due to the insulin deficiency of type 1 diabetes is painfully evident. There is no more dramatic reminder of weight loss as a prominent presenting feature of type 1 diabetes, especially if presentation is delayed. (b) The speed of restoration of body mass on replacing insulin is impressive. Source: Reproduced with permission from Eli Lilly & Co.

Table 24.1 Clinical features at presentation of type 1 diabetes, type 2 diabetes, and monogenic diabetes.

	Type 1 diabetes	Type 2 diabetes	Monogenic diabetes	Pancreatic
Weight loss	Yes (not essential, e.g. in slow-onset type 1 diabetes)	Usually no	No	Possible. If marked consider pancreatic carcinoma
Ketone formation	Yes (not essential in slow-onset type 1 diabetes)	Unusual, but may occur in ketosis-prone type 2 diabetes	No, unless recent fasting	Yes, but not necessary for diagnosis
Time course of symptoms	Weeks or days	Months	Months	Weeks or months
Severity of symptoms (e.g. nocturia >3)	Can be marked	Variable, but not usually extreme unless fuelled by sugary drinks to assuage thirst	Not usually severe	Depends on clinical situation
Family history	Possibly of insulin dependence at a young age	Present in 30% with onset in adult life	Present in almost all with onset in childhood or adult life	Only by chance, except in association with haemochromatosis
Age	Peak age in preschool and teenage years, but can present at any age	Typically after the age of 20 yr	Childhood, adolescence, or adult	Usually middle aged and older

Note: This is a diagnostic guide, with exceptions because of specific circumstances. It is not exhaustive and does not include rarer forms of diabetes, including syndromic diabetes.

Weight loss

Establishing whether significant weight loss has occurred is the most important aspect of history taking in those with newly presenting diabetes. Unless secondary to concurrent disease, the symptom strongly suggests insulin deficiency and hence newly presenting type 1 diabetes. Its absence does not exclude type 1 diabetes, as the speed of onset of insulin deficiency and the presence of intercurrent illness, which may have exacerbated osmotic symptoms, may mean that weight loss has not yet commenced.

Weight loss at presentation of type 2 diabetes may occur from dietary restriction, often undertaken because of suspicion of impending health problems. Such deliberate changes in eating habit are readily established from the history. Typically, weight does not change, or even continues to rise, prior to the symptomatic onset of type 2 diabetes.

The weight loss mainly reflects the relative loss of the anabolic actions of insulin. Muscle wasting may be prominent, especially in young men. Associated loss of muscle strength may be reported. As an anabolic hormone, insulin acts principally to inhibit protein degradation [14]. Its relative absence allows the balance between continuous protein synthesis and breakdown to be disturbed. There is an additional effect of insulin deficiency in the failure of normal promotion of lipogenesis and inhibition of lipolysis. Excess non-esterified fatty acids accumulate in plasma, forming substrate for ketogenesis. If the clinical presentation of diabetes is acute, a component of the weight loss will reflect the loss of both intracellular and extracellular water.

Blurred vision

Major changes in plasma glucose will be followed over a period of days and weeks by blurring of vision. The symptom is typically present after a relatively acute glucose change, usually in the context of presentation of type 1 diabetes or in the specific circumstance of a hyperosmolar presentation of type 2 diabetes. It is most important to explain that the visual blurring will become worse following the relatively rapid correction of gross hyperglycaemia. This explanation is vital to avoid the supposition that diabetes-related blindness is already progressing, with consequent unnecessary worry. It also prevents the unnecessary purchase of spectacles that will be redundant once the hyperglycaemia is treated.

It is reasonably assumed that shifts in osmotic pressure between plasma and inside the eyeball account for the visual change. Certainly, this provides a practical and immediately understandable explanation. Detailed tests, however, have not tied down any identifiable refractive change [15].

Infections

Exposure of leucocytes to glucose concentrations above 11 mmol/l impairs phagocytic and other functions [16]. This effect, together with other possible effects on immune function (Chapter 61), explains the impaired ability to fight off bacterial and fungal infections. Susceptibility to viral infections appears to be little changed, although clear data are lacking.

Recurrent or refractory yeast infections may draw attention to previously undiagnosed diabetes. Most frequently this involves vaginal candidiasis in women or balanitis in men. Normalization of blood glucose levels will permit clearance of the infection with continued antifungal application. Staphylococcal pustules, boils, and carbuncles may be present at the diagnosis of diabetes, especially type 1 diabetes. This clinical observation was supported by a prospective study of 482 individuals with skin or mucous membrane sepsis presenting to an accident and emergency department who were found to have a greater than threefold increased incidence of capillary blood glucose >7.8 mmol/l compared with a background population [17].

Very rare but serious infective presentations of diabetes must be considered. Necrotizing fasciitis is considerably more common in people with diagnosed and undiagnosed diabetes [18]. Fournier gangrene (gangrene of the perineum and genitalia) is associated with diabetes in almost 50% of cases [19]. The rare and often fatal facial and/or maxillary sinus fungal infection mucormycosis is most often associated with diabetes [20].

The important new topic of susceptibility of people with diabetes to more severe illness with Covid-19 is considered later.

Diabetic ketoacidosis

DKA occurs as a result of marked insulin deficiency associated with an increase in circulating levels of counter-regulatory hormones. It is characterized by hyperglycaemia, acidosis, and ketosis (identified by the presence of ketonuria or ketonaemia). It mainly occurs in people with type 1 diabetes, but it is not uncommon in type 2 diabetes. Ketosis-prone type 2 diabetes tends to be more common in older, overweight, people of other-than-white ethnicity, and DKA may be their first presentation of diabetes [21].

The prevalence of DKA at initial disease presentation in children and young people is well documented [22] and remains high – data from the registry component of the SEARCH for Diabetes in Youth Study reported a prevalence of 29–31% in 2002–2010, with those from other-than-white ethnic backgrounds and a low income threshold more likely to be affected [23]. In adults, data from the UK National Diabetes audit showed that while nearly 4% of people with type 1 diabetes experience DKA each year, only about 6% of cases of DKA occur in adults newly presenting with type 1 diabetes [24]. The overall mortality rate from DKA ranges from 2% to 5%, but is higher in older people.

DKA typically presents with the symptoms of hyperglycaemia (i.e. thirst, polyuria, and polydipsia). Other symptoms include malaise or lethargy and muscle cramps. Abdominal pain and vomiting may be sufficiently severe to mimic an acute surgical problem. It is critically important to recognize this, as the administration of an anaesthetic is almost invariably fatal. All doctors dealing with emergencies should be aware of the potential pitfall of missing this tell-tale sign of DKA.

Clinical signs include dehydration, deep sighing respirations (air hunger or Kussmaul respiration), and a sweet-smelling fetor (like nail varnish remover) caused by the ketones on the breath. As the ability to detect the smell of ketones is genetically determined, and approximately one-third of people are unable to do this, it is important that individual doctors are aware if they are not equipped with this additional diagnostic tool. Consciousness may be clouded. If the condition has progressed to the stage of coma, the associated signs of dehydration must lead to urgent checking of blood glucose and urinary or blood ketones and blood pH to expedite definitive treatment. If bedside

blood ketone testing is not available, then the semi-quantitative urine test to detect +++ ketonuria is entirely satisfactory.

The marked deficiency or absence of insulin in this condition means that insulin-mediated glucose uptake into tissues such as muscle and fat cannot occur and hepatic glucose output is unrestrained. In the meantime, the dysregulated secretion of counter-regulatory hormones (glucagon, growth hormone, and catecholamines) enhances the breakdown of triglyceride into free fatty acids and increases the rate of gluconeogenesis, which is the main cause for the high blood glucose level in diabetic ketoacidosis. β-oxidation of these free fatty acids leads to the formation of ketone bodies (β-hydroxybutyrate, acetoacetate, and acetone). Acetone is volatile and is released from the lungs, giving the characteristic sweet smell to the breath. Metabolic acidosis ensues when the ketone bodies are released into the circulation and deplete the acid buffers.

The hyperglycaemia-induced osmotic diuresis further depletes sodium, potassium, phosphates, and water. Individuals with DKA are often profoundly dehydrated and have a significantly depleted total body potassium at presentation. Sometimes, a normal or even elevated serum potassium level is seen as a result of the extracellular shift of potassium with severe acidosis. Great care must be taken to monitor serum potassium levels repeatedly once insulin treatment is started, as the concentration can drop precipitously (Chapter 41).

Hyperosmolar hyperglycaemic syndrome

HHS occurs exclusively in people with type 2 diabetes. Often there is a history of several days of ill health, in contrast to DKA, which presents within hours of onset. The principal clinical feature in HHS is profound dehydration. Confusion is usual, and focal neurological symptoms such as weakness on one side or hemi-sensory abnormalities may develop and be easily confused with stroke. HHS was previously termed hyperosmolar non-ketotic (HONK) coma. This terminology has been changed, as coma is a relatively rare feature (<10%) and mild ketosis may be present at diagnosis (sometimes leading to misdiagnosis of ketoacidosis).

HHS shares many features in common with DKA, the major exceptions being the absence of significant ketoacidosis. This is likely because of the residual low-level insulin secretion, which suppresses lipolysis sufficiently to avert ketogenesis, but not sufficiently to prevent hyperglycaemia. Additionally, hyperosmolarity itself may decrease lipolysis, limiting the amount of free fatty acids available for ketogenesis. HHS accounts for 10–30% of hyperglycaemic emergencies. As the prevalence of type 2 diabetes rises inexorably, it is becoming an increasingly common hospital admission and presenting in ever-younger adults and teenagers [25]. Up to two-thirds of those affected have not previously been diagnosed as having diabetes. Mortality rates in HHS have been reported to be 5–20%, a rate that is 10-fold higher than that reported for DKA [26,27] and increases significantly when the patient is above the age of 70 years.

Macrovascular presentations

Acute coronary syndromes

As the risk of ischaemic heart disease is linearly related to fasting and post-prandial blood glucose concentrations, it is unsurprising that both impaired glucose tolerance and diabetes are over-represented in populations presenting with acute coronary syndromes, which include acute myocardial infarction and unstable angina [28]. Consequently, type 2 diabetes frequently presents for the first time at hospitalization with acute coronary syndromes. This presentation is complicated by stress hyperglycaemia resulting from elevations of catecholamines and cortisol. Stress hyperglycaemia is defined as 'hyperglycaemia resolving spontaneously after dissipation of an acute illness', which can also occur in people with pre-existing diabetes [29]. Although this may cause problems for the purist wishing to evaluate an effect of diabetes *per se*, from the perspective of the patient with a life-threatening condition exacerbated by dysglycaemia, exact definitions of diabetes are irrelevant. Stress hyperglycaemia and established diabetes have similarly increased mortality from myocardial infarction. In a New York municipal hospital cohort of individuals with acute myocardial infarction, three-year mortality was 52% in those with stress hyperglycaemia (defined as admission blood glucose >7.0 mmol/l) compared with 42% in those with diabetes [30]. The three-year death rate in those with normal glucose levels was 24% in the same study. A meta-analysis has confirmed this effect, with a 3.9-fold increased risk of death associated with stress hyperglycaemia, compared with a 1.7-fold increased risk of death associated with established diabetes [31]. In this context, one of the most important findings of the Diabetes mellitus Insulin Glucose infusion in Acute Myocardial Infarction (DIGAMI) study is often overlooked. The effect of reasonable glycaemic management (blood glucose <10 mmol/l) for those with no prior insulin therapy and stratified as having low coronary risk factors produced a 52% improvement in mortality [32]. This group would have included those with stress hyperglycaemia. In contrast, the DIGAMI study showed no significant benefit of acute blood glucose control for individuals previously treated with insulin.

Estimates of the incidence of stress hyperglycaemia at presentation of acute coronary syndromes range from 10% to 16% [33,34]. This compares with estimates of the prevalence of diabetes at presentation of myocardial infarction of 10–24% [35,36]. Variation in these figures is likely to reflect the influence of racial affiliation on the prevalence of pre-diabetes and type 2 diabetes in the population, as well as increased awareness and effective screening processes to identify previously undiagnosed type 2 diabetes.

Good clinical practice demands measurement of plasma glucose on diagnosis of an acute coronary syndrome. If plasma glucose is raised (7 mmol/l may be quoted, but in the individual case interpretation depends on time since last meal), then both fasting plasma glucose and glycated haemoglobin (HbA_{1c}) should be measured. Raised plasma glucose should indicate a need for particular attention to adequate glucose management during the acute event. Given that the HbA_{1c} result is unlikely to be available immediately, hyperglycaemia indicates a need for rapid control in the acute situation when the first few hours are critical. A fasting plasma glucose of >5.6 mmol/l during the acute admission and/or an admission plasma glucose of >7.8 mmol/l yielded a sensitivity of almost 90% and a positive predictive value of 44% for detecting diabetes [37].

Where there is diagnostic uncertainty, targeted screening in the post-acute setting with a standard 75 g oral glucose tolerance test (OGTT) is acceptable. But when is the optimal time to perform this test? In a group of individuals with myocardial infarction and no previous diagnosis of diabetes, both pre-discharge and six weeks post-discharge OGTTs were performed, showing a good correlation between the two OGTTs [38]. There was 49% concordance between classifications to which an individual was assigned in both OGTTs. The best predictor of abnormal glucose handling

(impaired glucose tolerance or diabetes) being diagnosed at three months was observed to be the 60-minute blood glucose level during the pre-discharge OGTT. The National Institute of Health and Care Excellence (NICE) guideline (2020) recommends that all individuals with acute coronary syndrome and admission blood glucose >11.0 mmol/l should have fasting plasma glucose no earlier than day 4 after the onset of the acute coronary event or have an HbA_{1c} test before discharge [39].

Acute stroke

The prevalence of previously diagnosed diabetes in individuals with acute stroke is 8–28%, but an additional 6–42% have unrecognised pre-existing dysglycaemia [40]. Plasma glucose at presentation is a major prognostic factor. One series of 86 individuals with acute stroke demonstrated that full functional recovery at four weeks was only seen with those with presenting blood glucose levels <8 mmol/l [41]. The extent to which this reflects the metabolic stress response in proportion to the severity of the cerebrovascular insult as opposed to hyperglycaemia itself impairing subsequent recovery from ischaemic damage cannot be ascertained from these observational data.

The observations on poorer outcome in those with stress hyperglycaemia following myocardial infarction have been reproduced in respect of acute stroke disease. In a systematic review of observational studies examining the prognostic significance of hyperglycaemia in acute stroke, the unadjusted relative risk of in-hospital or 30-day mortality was 3.07 (95% confidence interval [CI] 2.50 to 3.79) in people without diabetes but with admission plasma glucose level >6–8 mmol/l and 1.30 (95% CI 0.49 to 3.43) in those with known diabetes [42]. The relative risk of poor functional outcome in hyperglycaemic individuals without diabetes was 1.41 (95% CI 1.16 to 1.73). Sudden increases in plasma glucose levels appear to impair tissue function more in those individuals who have not been habituated to hyperglycaemia.

Persistent hyperglycaemia (defined as blood glucose >7.0 mmol/l) in the 72 hours after acute stroke is associated with an increase in infarct size, measured using magnetic resonance imaging, and worse stroke outcome [43]. Nonetheless, currently there are no satisfactory outcome studies of control of plasma glucose on the outcome of stroke [44]. The largest study to date, which included 993 individuals, failed to achieve normalized plasma glucose at 24 hours [45]. Importantly, no assessment has yet been conducted of plasma glucose management during the first few hours after presentation with acute stroke, and it is likely that it is in this window of time that this particular presentation of hyperglycaemia may most beneficially be managed.

Microvascular presentations

Eye presentations

Symptomatic loss of vision may occasionally be the presenting feature of type 2 diabetes, where hyperglycaemia has been present for an uncertain number of years, silently causing tissue damage and retinopathy. Loss of vision as a diagnostic event is most often a consequence of macula oedema, but may also be secondary to vitreous haemorrhage. Central or branch retinal vein occlusion is more common in diabetes and may also cause symptomatic presentation of the condition.

Around the time of diagnosis of type 2 diabetes, marked retinopathy with cotton-wool spots or intraretinal microvascular abnormalities was present in 8% of men and 4% of women in the UK Prospective Diabetes Study (UKPDS) [46]. The critical importance of arranging full retinal examination, preferably by digital retinal imaging, is illustrated in Figure 24.2. Approximately 1% of individuals presenting with symptomatic type 2 diabetes have sight-threatening retinopathy at that time. Very early recognition is essential, as the initial treatment of the diabetes will decrease blood glucose levels, cause retinal blood flow to return acutely to normal levels, and may result in marked worsening of the retinopathy.

In the UKPDS, the severity of retinopathy was related to higher fasting plasma glucose levels. In addition, in men increased alcohol consumption was related to increased severity of retinopathy, while leaner women had more severe eye lesions. Visual acuity was normal in most individuals, but in men there was a trend for those with more severe retinal lesions to have worse visual acuity.

The potential severity of diabetic retinopathy at the time of diagnosis of type 2 diabetes is illustrated by the observation that 15% of those with moderate background retinopathy progress to require photocoagulation therapy within three years [47]. The specific reason for photocoagulation therapy was maculopathy alone in 72% and proliferative retinopathy in 11% in this group of individuals

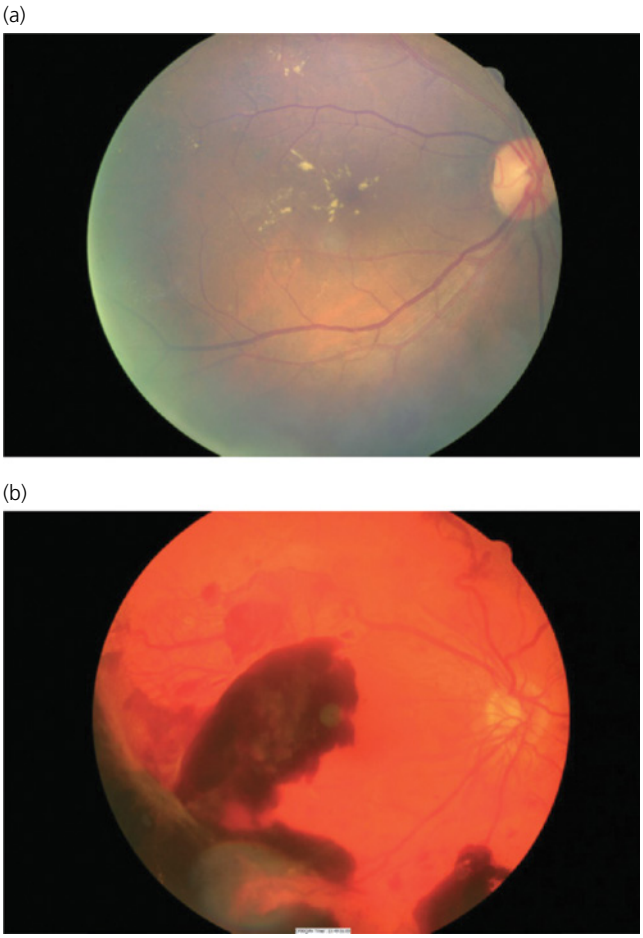

Figure 24.2 (a) Immediate laser therapy was required for the macular oedema associated with the severe exudative maculopathy present at the time of diagnosis. (b) New vessels are present, arising both from the optic disk and from the peripheral retina. Bleeding from the latter caused the prominent pre-retinal haemorrhages that obscure the fovea and in this case caused presentation because of loss of visual acuity.

with type 2 diabetes. Although it is likely that the prevalence of retinopathy of all grades of severity is lower if type 2 diabetes is diagnosed at routine screening rather than symptomatic presentation, this has yet to be quantified.

Diabetes kidney disease

Approximately 20–40% of all people with diabetes develop diabetes kidney disease [48]. In type 1 diabetes, 20–30% will have moderately increased albuminuria after a mean duration of 15 years of diabetes [49, 50], but it is unlikely to be present at diagnosis. In contrast, diabetes kidney disease may be present at diagnosis of type 2 diabetes or shortly thereafter, as diabetes may have been present for many years before the actual diagnosis.

Data from the US National Health and Nutrition Examination Survey (NHANES) 1992–2002 found that those with undiagnosed diabetes had a prevalence of nephropathy of 26.5%, determined from a spot urine albumin–creatinine ratio [51]. Similarly high prevalence of microalbuminuria was reported in the UKPDS in UK and the Hoorn Screening Study in Dutch populations [52, 53]. The prevalence of microalbuminuria has also been reported to be high in pre-diabetes [54, 55].

Although rare as a presenting feature for type 2 diabetes, the observation of unexplained albuminuria should lead to tests for hyperglycaemia.

Neuropathic syndromes

Although any of the neuropathic syndromes of diabetes may precipitate the initial presentation, symmetrical distal sensory neuropathy, mononeuropathies, and amyotrophy are the most likely candidates. The possibility of diabetes underlying most presentations of neurological symptoms must be considered.

Diffuse symmetrical sensory neuropathy is the most common neuropathy. A precise estimate of the true prevalence of this neuropathy has been difficult to ascertain, and reports vary from 7% to 60% in people with diabetes, depending on the criteria and methods used to define the neuropathy [56, 57]. The prevalence increases with both age and duration of diabetes. At 12-year follow-up in the UKPDS, 64% of men and 44% of women who were free of neuropathy at baseline developed at least one neuropathic abnormality [58].

Any nerve may be affected by an acute diabetic mononeuropathy, but palsy of cranial nerves III, IV, VI, and VII presents most often. It is a rare mode of presentation of type 2 diabetes, but not type 1 diabetes.

Diabetic amyotrophy may present as weight loss, and unless pain in the thighs is prominent, the clinical picture may resemble that of malignant disease. Weakness of quadriceps, with visible wasting and absence of the knee tendon reflex, should allow recognition and lead to the measurement of plasma glucose. Such presentation is likely to be associated with type 2 diabetes, but again is rare.

Diabetes-related foot disease

A foot lesion can be a presenting sign of diabetes, and it is estimated that the lifetime risk of developing a foot ulcer in people with diabetes may be as high as 25% [59]. Presentation with a black toe is particularly associated with type 2 diabetes. Peripheral neuropathy leads to sensory motor and autonomic dysfunction, with loss of the protective pain sensation, dry skin, and callus formation. Loss of pain sensation in the feet is usually unnoticed and subsequent trauma does not come to attention until obvious injury is apparent. In approximately half of those with foot ulcers, concomitant peripheral arterial disease is present [60]. In the European Study Group on Diabetes and the Lower Extremity (EURODIALE) study, foot ulcers with peripheral arterial disease were associated with considerably lower healing rates, and higher major amputation and mortality rates [61].

Pregnancy

The time course of presentation of GDM may be predicted from knowledge of its pathogenesis. The key variable is the physiological insulin resistance that develops during pregnancy. Although several, necessarily small, studies have quantitated this, it is most clearly illustrated by the change in exogenous insulin requirements during pregnancy in women with type 1 diabetes. During steady glycaemic levels and food intake, insulin requirements do not change until ~18 weeks' gestation, whereafter there is a linear increase until around 28–30 weeks' gestation [62]. The extent of change varies between pregnancies from none to over a threefold increase, with an average increase in daily insulin dose of 40% [63]. The range is assumed to be a function of the placenta (fetal-derived tissue), as considerable variation is exhibited between successive pregnancies in the same woman. Predisposed women cannot mount an adequate β-cell response if the degree of insulin resistance becomes too great.

In the light of this information, it can be understood why the elevated blood glucose levels of GDM are not seen in the first half of pregnancy. Screening for GDM will be most sensitive later in pregnancy, but this sensitivity must be balanced with the opportunities to intervene. The current NICE guideline (2015, updated December 2020) on diabetes in pregnancy therefore recommends testing at 24–28 weeks' gestation of women with risk factors [64].

Even mild degrees of elevation of plasma glucose may be deleterious to the fetus, and these are far less than those that could produce osmotic symptoms. The multinational Hyperglycaemic and Pregnancy Outcome (HAPO) study of over 23 000 women found a continuous linear relationship between maternal glucose and fetal growth, with no apparent threshold effect by which to easily guide precise values at which GDM should be diagnosed [65]. Screening for GDM is therefore essential. Symptomatic presentation of GDM is unusual in the context of a healthcare system that provides universal screening for GDM, as per the International Association of Diabetes and Pregnancy Study Group (IADPSG) consensus panel [66]. However, there are practical concerns about implementing universal screening with the one-step 75 g OGTT recommended by international consensus, as well as a lack of high-quality health economic analysis of the costs of delivering the lifestyle and pharmaceutical interventions and benefits.

Where osmotic symptoms and superficial fungal infections are part of the clinical presentation, however, it is important to ask whether this is new-onset type 1 diabetes or type 2 diabetes. The former tends to be associated with higher plasma glucose levels and ketonuria. Both are associated with clearly elevated HbA_{1c} levels, as the hyperglycaemia has been present for several weeks or months. If the presentation is in the first half of pregnancy, it is likely that it will not remit after delivery. If the presentation is in the first half of pregnancy and is associated with raised HbA_{1c}, then a diagnosis of pre-existing diabetes may confidently be made and discussed with the woman [67].

Following one pregnancy complicated by GDM, although increased, the risk of recurrence in a subsequent pregnancy is far from certain, reflecting the variation in insulin resistance in successive

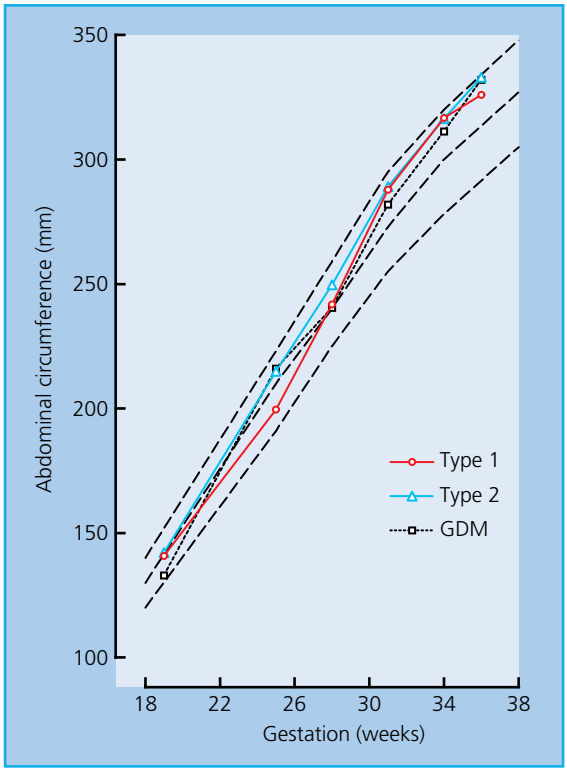

Figure 24.3 Similar rates of increase in fetal abdominal circumference in gestational diabetes (GDM) and pre-gestational diabetes as measured by ultrasound. Source: Reproduced from Lim et al. 2009 [67], with permission from RSM Journals.

pregnancies as the latter is determined by the placenta – tissue that is individual to the fetus. Higher rates have been reported in South Asian and Hispanic populations, as would be expected from the higher background prevalence of type 2 diabetes (52–69%) [68]. The importance of detection and treatment of GDM is reflected by the data shown in Figure 24.3. The rate of intrauterine growth is as rapid in GDM, as it is in type 1 diabetes and type 2 diabetes [67]. Early diagnosis of GDM carries major advantages for mother and child. The risk of developing subsequent diabetes in those with GDM ranges from 2.6% to 70% over periods from 6 weeks to 28 years [69]. The NICE guidelines for diabetes in pregnancy recommend that blood glucose should be tested prior to discharge to rule out persisting hyperglycaemia, then fasting plasma glucose should be performed at 6–13 weeks (or HbA_{1c} after 13 weeks if a fasting plasma glucose is not possible) and an annual HbA_{1c} test for those women with GDM who have a negative postnatal test for diabetes [64]. This will miss a proportion of women with normal fasting plasma glucose and impaired glucose tolerance, but it should be noted that the occurrence of GDM should itself be the trigger to advise vigorous lifestyle change and weight loss in particular.

Screening

It has been estimated from the 2002 US NHANES that one-third of the 13.3 million US adults with diabetes remained undiagnosed [70]. A similar estimate has been made for the UK [71]. Figures based on the Diabetes Prevalence Model by Public Health England estimated that in 2015 there were 3.8 million people aged 16 years and over diagnosed with diabetes in the UK, but that 940 000 had undiagnosed diabetes. Universal screening has not been implemented in the UK, as criteria for cost-effective and clinically effective screening are not met. NICE (2012, updated September 2017) recommends a two-stage strategy to identify people at high risk of type 2 diabetes (and those with undiagnosed type 2 diabetes) whereby a risk assessment is carried out first, and then where necessary a blood test offered to confirm whether type 2 diabetes or pre-diabetes is present [72]. People at risk can be identified using a validated computer-based risk-assessment tool from primary care electronic health records or from validated self-assessment questionnaires for individuals over the age of 40 years, people of South Asian and Chinese descent aged 25–39 years, and any adults with conditions that increase the risk of type 2 diabetes, other than pregnant women. Individuals with high-risk scores should then have fasting plasma glucose or HbA_{1c} tested, which will determine risk of progression to type 2 diabetes or identify possible type 2 diabetes. Fasting plasma glucose ≥7.0 mmol/l or HbA_{1c} ≥48 mmol/mol (6.5%) indicates the need for a second test to diagnose type 2 diabetes. Those with fasting plasma glucose of 5.5–6.9 mmol/l or HbA_{1c} 42–47 mmol/l (6.0–6.4%) are deemed as having high risk, and the recommendation is for them to be the managed as for pre-diabetes with an intensive lifestyle-change programme.

Fasting glucose, two-hour post-challenge glucose, and HbA_{1c} all equally predict the future microvascular complications of diabetes and can be considered diagnostic as well as screening tests [73]. The use of the concept of *impaired fasting glucose* with a cut-off of 5.5 mmol/l offers a simple way of excluding or demonstrating dysglycaemia [74]. Urinalysis for glycosuria has a high specificity (96–100%) but a low sensitivity (16–43%). Testing random blood glucose is specific but insensitive [75].

The population of individuals with early type 2 diabetes who are identified by any screening procedure differs considerably from those who present symptomatically. They are less likely to have established microvascular or macrovascular complications of diabetes. Attitudes to health may differ. The diagnosis will be less welcome, as it does not point the way to relief of symptoms and may not be accepted as important for future health. Following therapeutic advice concerning weight, diet, and physical activity may not be as assiduous as after a symptomatic presentation. For these reasons, a more careful approach to discussing the need for future action is required, with appropriately sensitive follow-up by the diabetes team.

Covid-19 and diabetes

Recently, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes coronavirus disease 2019 (Covid-19), has spread rapidly throughout the world in an unprecedented outbreak (Chapter 61). It was first reported in Wuhan, China, in December 2019 and as of 12 July 2023 there had been 767 972 961 globally confirmed cases of Covid-19 reported on the World Health Organization Covid-19 dashboard (https://covid19.who.int), including 6 950 655 deaths. The overall mortality of COVID-19 is variable, ranging from 0.7% to 10.8% [76].

Factors such as increasing age, ethnicity, deprivation, and comorbidities are associated with increased Covid-related morbidity and mortality [77]. Diabetes itself has been identified as one of the most common comorbidities associated with Covid-19,

both predisposing to severe illness and onset being precipitated by the illness itself. This is not unexpected, since increases in hospitalization and intensive care unit admission in people with diabetes during the 2010 influenza A (H1N1) pandemic were observed, confirming the susceptibility of people with diabetes due to impaired immune response [78]. People with diabetes have worse clinical outcomes from Covid-19, in particular higher hospitalization rates and a twofold risk of death [79].

Covid-19 contributes to worsening of dysglycaemia in those with diabetes over and above that contributed by stress hyperglycaemia. Several case reports raise the question as to whether SARS-CoV-2 can trigger new-onset diabetes. One series found 29 hospitalized individuals who were not known to have diabetes who developed hyperglycaemia during Covid-19, some of whom had a normal HbA_{1c} on admission [80]. A recent meta-analysis showed a pooled proportion of 14.4% for newly diagnosed diabetes in hospitalized individuals with Covid-19 [81]. Another cohort study, however, found only 4.9% newly diagnosed cases in their hospitalized cohort [82].

Similarly, during the Covid-19 pandemic there has been an apparent increase in new-onset type 1 diabetes in children with evidence of SARS-CoV-2 infection or exposure [83]. This prompted a national survey by the UK Association of Children's Diabetes Clinicians, which found that the proportion of new-onset type 1 diabetes presenting with DKA during the pandemic was higher in 2020 than in previous years, with 20% of units reporting delayed presentations and a significant proportion presenting with severe DKA [84]. Reasons for the delay ranged from fear of acquiring SARS-CoV-2 infection to difficulty in contacting or accessing a medical provider for timely evaluation. This is in contrast to others who found no deviation from the projected numbers of children with newly diagnosed type 1 diabetes [85], but did find an increase in DKA and the severity of DKA episodes in children and adolescents [86].

The interplay between diabetes and Covid-19 is far from clear. Diabetes may contribute to increased disease severity via compromised innate immunity, exaggerated pro-inflammatory cytokine response, and low expression of angiotensin-converting enzyme (ACE-2), and the association with obesity will be additive. Covid-19 itself leads to worsening glycaemia in people with diabetes by a stress hyperglycaemia response, with augmentation of insulin resistance through cytokines as well as the effects of drugs used in the management of Covid-19 such as corticosteroids, and possible direct virus-mediated β-cell damage [87]. Mechanistic studies suggest that SARS-CoV-2 binds to the ACE-2 receptor proteins expressed in key metabolic organ and tissues including pancreatic β cells, adipose tissue, the small intestine, and the kidneys. This allows the virus to enter human cells and cause pleiotropic alterations of glucose metabolism.

There are still many uncertainties as to the magnitude of new-onset diabetes in Covid-19, whether the glucose perturbations will persist or resolve after the infection, and whether or not Covid-19 increases risk of future diabetes. The severe metabolic stress of the illness would be expected to cause insulin resistance and raise blood glucose levels markedly in those with pre-existing marginal β-cell function. The CoviDiab Registry has been recently launched to track and measure new cases of diabetes among people who have Covid-19 [88], with the hope of shedding more light on these uncertainties and on whether a bi-directional relationship between Covid-19 and diabetes truly exists.

Other presentations

Ants clustering around urine is a classic description of diabetes, although it is not clear how often this constitutes the presenting complaint today. Periodontal disease, especially aggressive periodontitis, is more common in those with diabetes and may occasionally be the presenting complaint (Chapter 56) [89]. Cataracts typically develop 10 years earlier in people with diabetes [90]. Altered taste or excess production of saliva has been reported as a presenting feature of diabetes [91].

Conclusion

The mode of presentation is enormously varied. Especially as the incidence of diabetes is rising in all age groups, both in the UK and worldwide [92], the onus is on healthcare professionals to diagnose the condition effectively. Failure to recognize presenting features of diabetes can be costly for the individual with diabetes and society.

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5 Managing the Person with Diabetes

25 The Aims of Diabetes Care

Katharine D. Barnard-Kelly[1] and Richard I.G. Holt[2,3]

[1] Southern Health NHS Foundation Trust, Southampton, UK
[2] Human Development and Health, University of Southampton, Faculty of Medicine, Southampton, UK
[3] Southampton National Institute for Health Research Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK

Key points

- People with diabetes are individuals who have a condition that has medical, psychological, personal, and social risk factors and consequences. They are not passive recipients of healthcare and are not defined by their disease state.
- Optimal diabetes management occurs when the multidisciplinary diabetes care team and the person with diabetes actively work together as equal partners to achieve diabetes-related goals.
- Life-threatening diabetes emergencies, such as diabetic ketoacidosis, must be effectively managed, and attention paid to their prevention.
- Acute symptoms of hyperglycaemia need to be addressed by careful pharmacological management and lifestyle modification support.
- Diabetes management is a balance between supporting short-term optimal glycaemic management and quality of life while at the same time reducing the risk of long-term complications. This is achieved through effective medical treatment of glycaemia, cardiovascular risk factor management, and appropriate psychosocial support and education.
- The time of diagnosis can be traumatic and is a key milestone in the management of diabetes when effective education, support, and treatment are needed. It is important to ensure parity of esteem, by valuing mental health equally with physical health.
- Regular lifelong contact between the person with diabetes and their healthcare team is essential in order to provide person-centred care to support healthy adjustment to, and coping with, the demands of this complex condition that changes throughout a person's life.
- Diabetes-related complications should be managed effectively if and when they present to reduce their morbidity.

Diabetes is a lifelong condition that for the majority is currently incurable. It is associated with premature mortality and morbidity, from an increased prevalence of macrovascular disease and microvascular complications affecting the kidney, nerve, and eye [1,2]. High-quality randomized trials have shown that improving glycaemic levels is associated with a reduction in microvascular complications [3–5], while a multifaceted approach to cardiovascular risk factors will reduce cardiovascular morbidity and mortality [6]. Addressing the psychosocial challenges faced by people with diabetes reduces psychological distress and improves self-management behaviours [7,8]. A holistic approach to supporting the person with diabetes in making choices based on the best evidence available and providing them with autonomy in consultations leads to greater self-care and improved metabolic management [9].

The person living with diabetes will spend the vast majority of their time managing their own diabetes and only an estimated 1% of their time in contact with healthcare professionals. Therefore, it is crucial to provide individuals with appropriate medical and psychosocial support to help them optimally self-manage their diabetes. It is important that the purposes of the consultation or other contacts with the diabetes healthcare team are well defined, with clear aims to make them relevant and useful. To ensure that the individual derives the maximum benefit from the time spent with their diabetes healthcare team, whether this is in a hospital, primary care, or community setting, the consultation should be collaborative, patient centred, and goal focused. In addition, telemedicine provision of diabetes care, via phone, video-conference, or email contact or through educational sessions outside a traditional clinic setting has proven effective [10].

This chapter provides an overview of the aims and philosophy of diabetes care. Separate aspects of care will be covered in greater detail in subsequent chapters. The aims of diabetes care and management to improve the quality of life of the person with diabetes are fourfold. Life-threatening diabetes emergencies, such as diabetic ketoacidosis or severe hypoglycaemia, should be managed effectively, including preventive measures. The acute manifestations of hyperglycaemia, such as polyuria and polydipsia, need to be addressed. In practice, these occupy only a minority of the work undertaken by diabetes healthcare professionals. Much of the focus of care is therefore directed towards minimizing the long-term complications through screening and working together with the person with diabetes to support improved glycaemic and cardiovascular risk factor management. This provides a challenge for the diabetes team, because people with type 2 diabetes often have no symptoms at the time of care, yet are asked to make lifestyle changes and take medications that may place a considerable burden on them. The fourth aim of care is to avoid iatrogenic side effects, such as hypoglycaemia, and relies on collaborative care planning with the person with diabetes.

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St Vincent declaration

During the 1980s, there was a transformation in the widely held perceptions of the roles of people with diabetes and philosophy of care. Instead of their being viewed as passive recipients of healthcare, there was an increasing recognition that people with diabetes are individuals with a condition that has medical, personal, and social consequences. During this time there was an increasing awareness and acceptance of the concept that each person with diabetes should take on part of the responsibility for their diabetes management and act as equal partners with healthcare professionals. In response to this paradigm shift, representatives of government health departments and organizations for people with diabetes from all European countries met with diabetes experts under the auspices of the Regional Offices of the World Health Organization (WHO) and the International Diabetes Federation (IDF) in the hillside town of St Vincent, Italy, on 10–12 October 1989. They unanimously agreed a series of recommendations for diabetes care and urged that action should be taken in all countries throughout Europe to implement them (Box 25.1) [9]. Since that time this philosophy of partnership working between people with diabetes and healthcare professionals has been adopted within individual nations' strategies to improve the quality of diabetes care.

Box 25.1 St Vincent declaration [11]

- Elaborate, initiate, and evaluate comprehensive programmes for detection and control of diabetes and of its complications, with self-care and community support as major components.
- Raise awareness in the population and among healthcare professionals of the present opportunities and the future needs for prevention of the complications of diabetes and of diabetes itself.
- Organize training and teaching in diabetes management and care for people of all ages with diabetes, for their families, friends, and working associates, and for the healthcare team.
- Ensure that care for children with diabetes is provided by individuals and teams specialized both in the management of diabetes and of children, and that families with a child with diabetes get the necessary social, economic, and emotional support.
- Reinforce existing centres of excellence in diabetes care, education, and research.
- Create new centres where the need and potential exist.
- Promote independence, equity, and self-sufficiency for all people with diabetes, children, adolescents, those in the working years of life, and the elderly.
- Remove hindrances to the fullest possible integration of people with diabetes into society.
- Implement effective measures for the prevention of costly complications:
  - Reduce new blindness due to diabetes by one-third or more.
  - Reduce numbers of people entering end-stage renal failure by at least one-third.
  - Reduce by one-half the rate of limb amputations.
  - Cut morbidity and mortality from coronary heart disease by vigorous programmes of risk factor reduction.
  - Achieve pregnancy outcomes in women with diabetes that approximate those of women without diabetes.
- Establish monitoring and control systems using state-of-the-art information technology for quality assurance of diabetes healthcare provision and for laboratory and technical procedures in diabetes diagnosis, treatment, and self-management.
- Promote European and international collaboration in programmes of diabetes research and development through national, regional, and WHO agencies and in active partnership with persons with diabetes and with diabetes organizations.
- Take urgent action in the spirit of the WHO programme 'Health for All', to establish joint machinery between WHO and IDF European Region, to initiate, accelerate, and facilitate the implementation of these recommendations.

Diabetes care team

The diabetes care team involves a multidisciplinary group of healthcare professionals who are available to support the person with diabetes (Figure 25.1). A key component of diabetes care is to ensure that the individual with diabetes is at the centre of the provision of care. This means that they should be an equal member of the diabetes care team, working together with the healthcare professionals. This relationship should be based on the exchange of information, advice, and education to enable the healthcare team to provide best practice–tailored support for the individual with diabetes so that they feel sufficiently empowered to manage their condition themselves. This approach ensures that the care offered is personalized appropriately for the individual and their circumstances.

The large number of diverse health professionals involved in the diabetes care team means that the roles and responsibilities of all must be clearly presented and agreed. It is often helpful for the person with diabetes if the key members of their diabetes care team are identified, as they will have more contact with some healthcare staff than others.

Most routine type 2 diabetes care takes place in a primary care setting, but some people who have complications or complex medical or psychological needs will require management and support in a specialist setting for some or all of their care [12]. The diabetes physician usually takes overall responsibility for the diabetes medical care, but other specialists may be involved, for example an ophthalmologist may be needed to examine the eyes carefully and treat diabetic retinopathy, if present. Diabetes care is multidisciplinary, involving doctors, nurses, and many allied healthcare professionals whose responsibility is to support the person living with diabetes in the management of their condition. A close collaboration between primary and secondary healthcare professionals and among specialists is needed to ensure that all involved are aware of the issues that are relevant to the individual with diabetes, and that care is integrated and coordinated across the wide range of disciplines involved. Ensuring the person with diabetes remains at the centre of care is likely to facilitate the collaboration.

Given the chronic nature of diabetes, continuity of care is essential. Ideally this should be provided by the same doctors and nurses from visit to visit, but where this is not possible, the healthcare team should have access to previous records so that they are fully aware

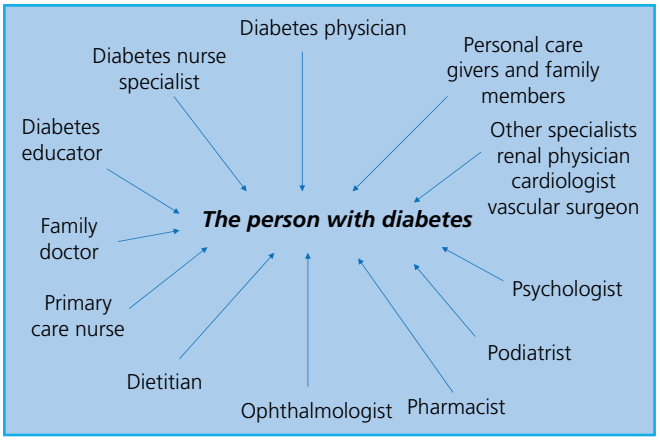

Figure 25.1 The multidisciplinary group of healthcare professionals who are available to support the person with diabetes.

of the medical history, background, and lived experience of the person with diabetes. In some developing countries this is particularly challenging, where medical records are often focused around single episodes of acute care of infectious diseases [13].

With the involvement of the person with diabetes in the diabetes team, the individual assumes several responsibilities. The task of implementing the day-to-day management plan of the diabetes lies with the individual; it may sometimes be difficult for healthcare professionals to accept this, particularly if their frame of reference is within an acute medical model of healthcare delivery. It is important to understand that diabetes self-management is challenging and so the diabetes care team should be available to support the person through their experiences with their condition. Diabetes distress, burnout, and impaired psychosocial functioning are all commonly reported by people with diabetes [14]. There have been increasing efforts to standardize psychosocial outcomes alongside biomedical outcomes. The recent US Food and Drug Administration Medical Device Development Tools (MDDT) qualification of the INSPIRE measures demonstrates the rigour now expected of psychosocial assessment in diabetes [15]. In addition, the International Consensus of Health Outcome Measures (ICHOM) produced a standard set of measure outcomes, biomedical and psychosocial, to promote robust assessment thereof across nations globally [16].

Adolescence can be a particularly challenging time, as this period of the person's life coincides with a time of rapid change, transition to adulthood, and increasing independence. Risk taking, experimentation, and increasing responsibility along the path to diabetes self-management by the adolescent are to be expected (Chapter 70).

Improving the outcome of the consultation

The time that a person with diabetes spends with a healthcare professional is limited and should be used as effectively as possible. Clinicians often give conflicting advice, both within the team and from one consultation to the next [9]. Goals are often not followed up, leaving the person with diabetes feeling frustrated. Studies have shown that typically physicians interrupt their patients 18 seconds after the patient starts to describe their problems, approximately half of patients' concerns are not discussed, and in half of consultations the patient and physician disagree on the central problem presented [9]. Such disagreement and inconsistency are associated with poorer outcomes. Better self-care and metabolic management are achieved through supporting the person with diabetes to make choices based on the best evidence available and providing autonomy in consultations. In the UK, the Department of Health has produced literature entitled 'Questions to ask' (Table 25.1), which provides guidance about the questions a person with diabetes might want to ask during a consultation to maximize the benefits from the visit to their healthcare team [17].

The consultation or educational programme should help the person with diabetes gain a clearer understanding of their condition and the behaviours required for optimal outcomes. This can only be achieved effectively when professionals and people with diabetes are enabled to work together. Taking a holistic approach, such as embodied in the Kaleidoscope model of care [9] (Figure 25.2), can facilitate this collaborative, patient-centred, joint goal-setting process.

The Kaleidoscope model of care presents a novel, holistic, tailored, and individualized approach to healthcare delivery for people with diabetes through an assessment of an individual's current

Table 25.1 Checklist of questions to ask your doctor at your appointment.

Tests, such as blood tests or scans
What are the tests for?
How and when will I get the results?
Who do I contact if I do not get the results?
Before your appointment
Write down your two or three most important questions.
List or bring all your medicines and pills – including vitamins and supplements.
Write down details of your symptoms, including when they started and what makes them better or worse.
Ask your hospital or surgery for an interpreter or communication support if needed.
Ask a friend or family member to come with you, if you like.
During your appointment
Do not be afraid to ask if you do not understand. For example 'Can you say that again? I still do not understand'.
If you do not understand any words, ask for them to be written down and explained.
Write things down or ask a family member or friend to take notes.
Before you leave your appointment
Check that:
You've covered everything on your list.
You understand, for example 'Can I just check I understood what you said?'
You know what should happen next – and when. Write it down.
Ask:
Who to contact if you have any more problems or questions.
About support groups and where to go for reliable information.
For copies of letters written about you – you are entitled to see these.
After your appointment, do not forget to
Write down what you discussed and what happens next. Keep your notes.
Book any tests that you can and put the dates in your diary.
Ask:
'What's happening if I'm not sent my appointment details?'
'Can I have the results of any tests?' (If you do not get the results when you expect – ask for them.) Ask what the results mean.

Source: Diabetes UK and Association of British Clinical Diabetologists 2005 [12].

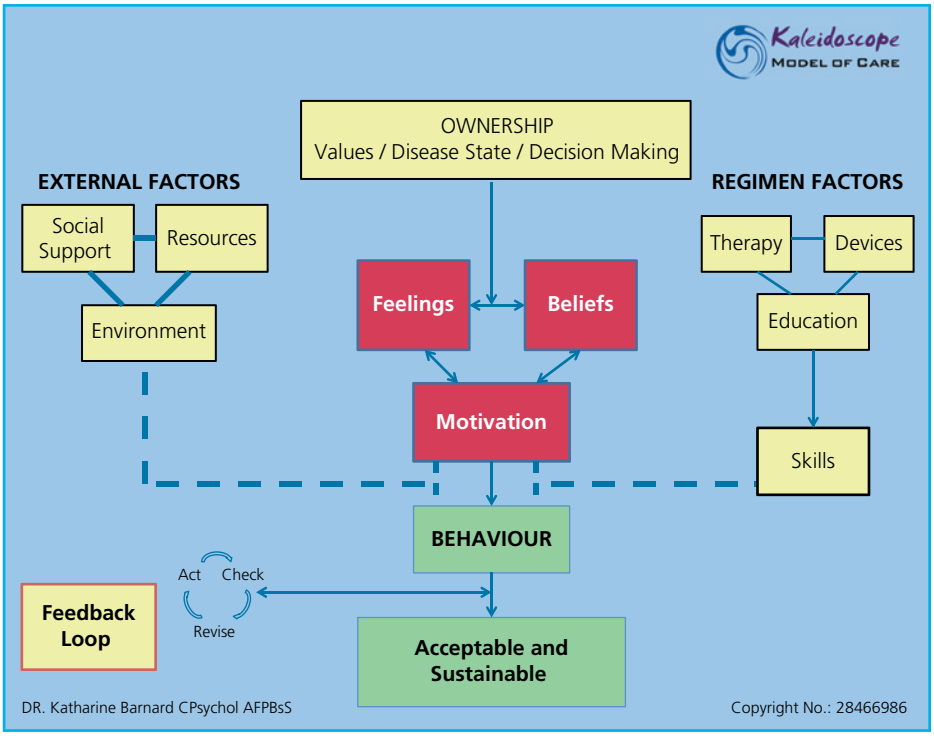

Figure 25.2 The Kaleidoscope model of care. Source: Barnard et al. 2014 [9].

regimen, barriers and motivation, and available support resources. It is flexible and applicable in different health settings, fundamentally promoting the specific needs of the individual with diabetes. These needs are dynamic, taking a different shape at different points in time, while recognizing and adapting to the range of care needed [9].

It is good practice to provide the person with diabetes with copies of any letters written about them [18,19]. Questions about treatment recommendations should be encouraged and people should be aware of what will happen next, including any requirement for further investigation. Regular review of management plans through joint dialogue, listening, discussion, and decision making between the individual and the healthcare professional, sometimes known as care planning, is the key to enhancing relationships and partnership working [20]. Contact details should be made available to enable the individual with diabetes to seek help if further questions arise.

In 2018 the UK National Health Service (NHS) published its 'Language matters: Language and diabetes' [21] document. This recognizes that the language used by healthcare professionals can have a 'profound impact on how people living with diabetes, and those who care for them, experience their condition and feel about living with it day-to-day'. The document sets out some basic principles for good practice for interactions between healthcare professionals and people living with diabetes. Furthermore, it lays out some common examples of language use and presents suggestions for alternative responses or ways to deal with them. Finally, the document encourages healthcare professionals to engage positively and avoid the use of negative language.

Following diagnosis

The period following the diagnosis of diabetes is crucial for the long-term management of diabetes. A huge amount of information and skills need to be assimilated by the person with diabetes at a time when they may be least able to do so, perhaps because of shock, denial of, or anger at the diagnosis [22]. Empathy and considerable skill are therefore needed to support the person with diabetes at this time. The diabetes team should perform a medical examination (usually the physician) and work with the individual to develop a programme of care that is individualized and includes treatment-oriented goals. Psychological support should be offered, and ongoing psychosocial assessment of coping, adjustment, and diabetes-related distress should be conducted.

Issues relating to diagnosis

The diagnosis of diabetes is based on the finding of one or more glucose values above internationally agreed values [23,24] (Chapter 2). Usually a diagnosis has been made prior to referral to the diabetes clinic, but this is not always the case. In the absence of symptoms, individuals require two glucose or glycated haemoglobin (HbA_{1c}) values above the diagnostic criteria to fulfil the diagnosis of diabetes.

Advice may be required to determine the type of diabetes, as the distinction is not always as clear as may be expected. When a young preschool child develops weight loss, polyuria, polydipsia, and ketoacidosis over a short period of time, the diagnosis is type 1 diabetes, while by contrast if an asymptomatic older overweight individual is found to be hyperglycaemic, the diagnosis is most likely to be type 2 diabetes (Chapter 24). These presentations lie at two ends of a spectrum, and the diagnosis of the type of diabetes may be less clear when the onset occurs in an overweight adult in their 30s who is found to have islet cell antibodies. Diabetes healthcare professionals should also be alert to the possibility of monogenic causes of diabetes (Chapter 20).

Although a precise diagnosis may not be needed from the outset, an early decision should be made about the necessity for insulin therapy (Chapter 24). While there may be clinical features that suggest the type of diabetes, time is often a useful diagnostic tool to determine whether the person with diabetes requires insulin.

Diabetes education

A key component to empower the person with diabetes is the provision of diabetes education [25] (Chapter 26). This information should be offered in a patient-centred manner, as it is retained more effectively when delivered in this way. Education may be provided individually or in a group setting.

It is essential that the person with diabetes understands their diabetes and develops the skills and competencies required to self-manage the condition as well as possible. People with newly diagnosed diabetes should have the chance to speak with a diabetes healthcare professional who can fully explain what diabetes is [26]. This will offer an opportunity to discuss the treatment and goals, as well as providing a practical demonstration of any equipment required to support self-management, for example blood glucose meters or insulin devices. The importance of ketones testing for those with type 1 diabetes should be explained. Where self-monitoring has been advocated, it is essential that the individual knows how to interpret the results and how to act appropriately in response to that information.

A qualified dietitian should provide advice about how to manage the relationships between food, activity, and treatment (Chapter 27). Where necessary, they should explain the links between diabetes and diet and the benefits of a healthy diet, exercise, and optimal diabetes management. As an essential member of an effective clinical care team, a diabetes specialist nurse or practice nurse also has a role in providing dietary advice together with relevant literature [26].

The social effects of diabetes should be discussed, as they may relate to employment, insurance, or driving (Chapter 66). Some countries require individuals with diabetes to inform the appropriate licensing authorities. Advice about diabetes and foot care should also be given (Chapter 53).

Although education is essential following diagnosis, it is important to appreciate that this is a lifelong process that should consider recent advances in medical science and changes in circumstances of the person with diabetes [25]. Education should be available via different modalities that best meet the needs of each individual.

The best measure of effective education is not simply that someone knows more, but rather that they are able to apply the new knowledge to enhance their diabetes self-management. The simple provision of knowledge by itself is often insufficient to influence behavioural change. High demands are placed on the person with diabetes regardless of the type of diabetes, especially when the benefits are not immediate, may only accrue with time, and even then may not be appreciated. The individual with diabetes needs to gain an understanding that improved glycaemic levels can help prevent the long-term complications of diabetes, such as a myocardial infarction or proliferative retinopathy, even though they may have never experienced these conditions.

The diagnosis of diabetes may provoke a grief reaction and the diabetes team needs to support the person with diabetes as they work through this (Box 25.2). Efforts should be made to help the individual adapt to their new reality of living with diabetes and engage in optimal self-management. If this does not happen, they can be left feeling overwhelmed by diabetes or expect that their healthcare team can take control for them. For some it may take a very long time to accept their diabetes and the demands placed on their life. Therefore, emotional and psychological support and techniques need to be available in the long term and should be discussed at every clinic appointment.

People with newly diagnosed diabetes often want to speak with others who have diabetes or who have had similar experiences while developing diabetes. Many countries have diabetes-related charities that can provide this support, and it is important that information about what help is available, including local centres or peer support groups, is provided in a timely fashion.

Box 25.2 Case study

Dave is 25 years old and recently diagnosed with type 1 diabetes. The diagnosis was made following an acute admission to hospital with diabetic ketoacidosis and insulin therapy was initiated.

Initially appearing to accept the diagnosis, Dave quickly became very angry about his perceived loss of control over his life and the reduction in his quality of life because of the new demands placed by diabetes and its treatment. Feeling guilty about whether he could have prevented it, and despairing about the lifelong condition, Dave found it increasingly difficult to keep up with the daily tasks of self-management, which in turn contributed to his feelings of despair and loss of control.

The healthcare team helped Dave identify some short-term goals for diabetes self-management and signposted social media support online, including on Twitter, as well as a local support group. Dave and his healthcare team worked together on problem-solving techniques to help make some of the diabetes tasks more achievable in his daily routine.

Ongoing clinic visits

The diabetes team needs to work to together with the person with diabetes to review the programme of care, including the management goals and targets at each visit [27]. It is important that the individual shares equally in all treatment decisions, as this improves the chances of jointly agreed goals being adopted following the consultation. 'No decision about me without me' is central to the NHS philosophy [28]. A family member, friend, or carer should be encouraged to attend the clinic appointment to support the person with diabetes, and to stay abreast of developments in diabetes care [29].

An important goal of management is to prevent the microvascular and macrovascular complications of diabetes without inducing iatrogenic side effects. This involves active management of hyperglycaemia together with a multifaceted approach targeting other cardiovascular risk factors. Ensuring parity of esteem by valuing mental health equally with physical health is crucial at all times. Funding, commissioning, and training should be on a par for both physical and mental health services [30].

Glycaemic management

It is important to enquire about and discuss hyperglycaemic symptoms and problems with medications, including issues relating to injections, hypoglycaemia, and self-monitoring of blood glucose.

Hyperglycaemic symptoms

Symptoms relating to hyperglycaemia usually occur when the blood glucose rises above the renal threshold, leading to an osmotic diuresis. Polyuria, particularly at night, polydipsia, and tiredness may ensue. General malaise may also occur and is not always ascribed to the hyperglycaemia.

Medications

The diabetes care team is responsible for ensuring that the person with diabetes has access to the medication and equipment necessary for diabetes management. In many, but not all, countries this is available for free or at a reduced rate; many people with diabetes may be unaware of this and timely advice may alleviate some of the anxieties about the cost of diabetes.

Oral glucose-lowering drugs

Each of the oral glucose-lowering drugs has its strengths and profile of side effects (Chapter 35) and these should be discussed. Strategies may be devised to maximize the tolerability of diabetes medications. For example, the timing of metformin in relationship to meals, or the use of long-acting preparations, may reduce the risk of gastrointestinal upset. Where treatments are not being tolerated, these should be changed in order to facilitate improved medication taking. Another example is the need to discuss the risks of hypoglycaemia with sulfonylureas.

Insulin

Insulin therapy is complex: it must be given by self-injection or pump and there is considerable variation in the doses, regimens, and devices available to people with diabetes. In addition, the use of continuous glucose monitoring and closed-loop systems by people with type 1 diabetes require discussion on suitability, use, and effectiveness. It is important that during the clinic visit, the individual has an opportunity to discuss injection technique and any difficulties with injection sites, which should be examined at least annually. Information about the appropriate storage of insulin and safe disposal of sharps (needles) is needed.

The commonest side effects of insulin are hypoglycaemia and weight gain (Chapter 31). In addition to these, there are a number of other issues that should be addressed including injection site problems, such as lipohypertrophy, and device and needle problems.

Assessment of glucose levels

Supporting the person with diabetes to achieve optimal glycaemic levels is a vital component of diabetes care. The methods of assessing glucose levels essentially involve short-term measures, such as self-monitoring of blood glucose, and long-term measures, such as HbA_{1c} (Chapter 29). Not all people with diabetes will need to undertake self-monitoring of blood glucose, but where they do it is incumbent on the healthcare professional to discuss with them the findings and how these will affect future management. The HbA_{1c} provides a measure of the longer-term adequacy of glycaemic management and sometimes there may be a discrepancy between this measure and self-monitored blood glucose. It is important to explore the reasons that underlie the differences, which may range from biological issues, such as genetically determined rates of glycation, through inappropriately timed glucose readings to fabricated results. A pristine sheet (with no blood stains from finger-sticks) and the use of a single pen colour may be a clue to the latter. It is important to explore in a non-judgmental way why the individual might engage in such a practice. This could reflect a poor relationship with the healthcare team or potential psychosocial challenges with disease and self-management. The use of computers and the ability to download results may help to observe patterns of hypo- and hyperglycaemia, although it is important to make sure that the meter has not been shared. Increasingly it is possible to use the internet to review glucose remotely.

People with diabetes must be supported in an open and non-judgmental way. Sometimes clinicians can appear to show the opposite, which is unhelpful and counter-productive to joint goal setting and collaborative consultation. Feeling reprimanded or misunderstood can be frustrating and upsetting, and it is understandable why someone would not choose to put themselves through the experience if they did not have to. It is better to build a relationship whereby the person with diabetes feels that the healthcare professional is there to support them and work together to find solutions and overcome barriers to optimal self-management. It must be remembered that the chronic nature of diabetes means there is never, nor will there ever be, a day off self-management. This can be exhausting and feel relentless to those living with the condition. Empathy and understanding go a long way in building positive, enduring therapeutic relationships.

The Diabetes Control and Complications Trial and the UK Prospective Diabetes Study (UKPDS) have clearly established that lower levels of glycaemia are associated with reduced risk of long-term microvascular complications in type 1 diabetes and type 2 diabetes, respectively [3–5]. For this reason, learned societies such as the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) and government bodies such as the National Institute for Health and Care Excellence (NICE) have set tight glycaemic targets to minimize the risk of complications for individuals with diabetes [31–33]. Furthermore, in the UK general practitioners are incentivized financially to achieve tight glycaemic levels for their patients. However, there has been an increasing awareness of the need to individualize targets for the person with diabetes, depending on factors such as life expectancy, duration of diabetes, comorbidity including cardiovascular disease, resources, and availability of support (Figure 25.3).

The natural history of the development of complications is long and, in some situations, may be longer than the life expectancy of the person with diabetes. It would be a poor trade to insist on switching a frail, complication-free 90-year-old person to insulin if they subsequently fell and broke their hip or died as a result of insulin-induced hypoglycaemia. Less melodramatic but still important is the consideration about dietary and lifestyle change in people with low risk of disabling complications: is it really necessary to deny an older person with diabetes a piece of birthday cake if this is one of the few food pleasures in their life? A more sensible approach would be to advise a limit to portion size, rather than insist on severe dietary restriction.

Although there is an appropriate clinical emphasis on glycaemic targets, the results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [35], the Action in Diabetes and Vascular disease: preterAz and diamicroN MR Controlled Evaluation (ADVANCE) trial [36], and the Veterans Affairs Diabetes Trial (VA-DT) have led to a note of caution [37]. These trials have shown that tight glycaemic management in people with a longer duration of diabetes did not prolong life. In the case of the ACCORD trial, increased cardiovascular mortality was seen in those receiving intensive glycaemic management [35]. Again, these findings highlight the need for individualized targets.

Despite clinical guidance and the availability of effective treatments, many people with diabetes are unable to achieve the desired glycaemic levels. It is important for the healthcare professional to explore the reasons why this might be the case together with the individual. Advice about adjustment of treatment or further education or psychological support may be needed.

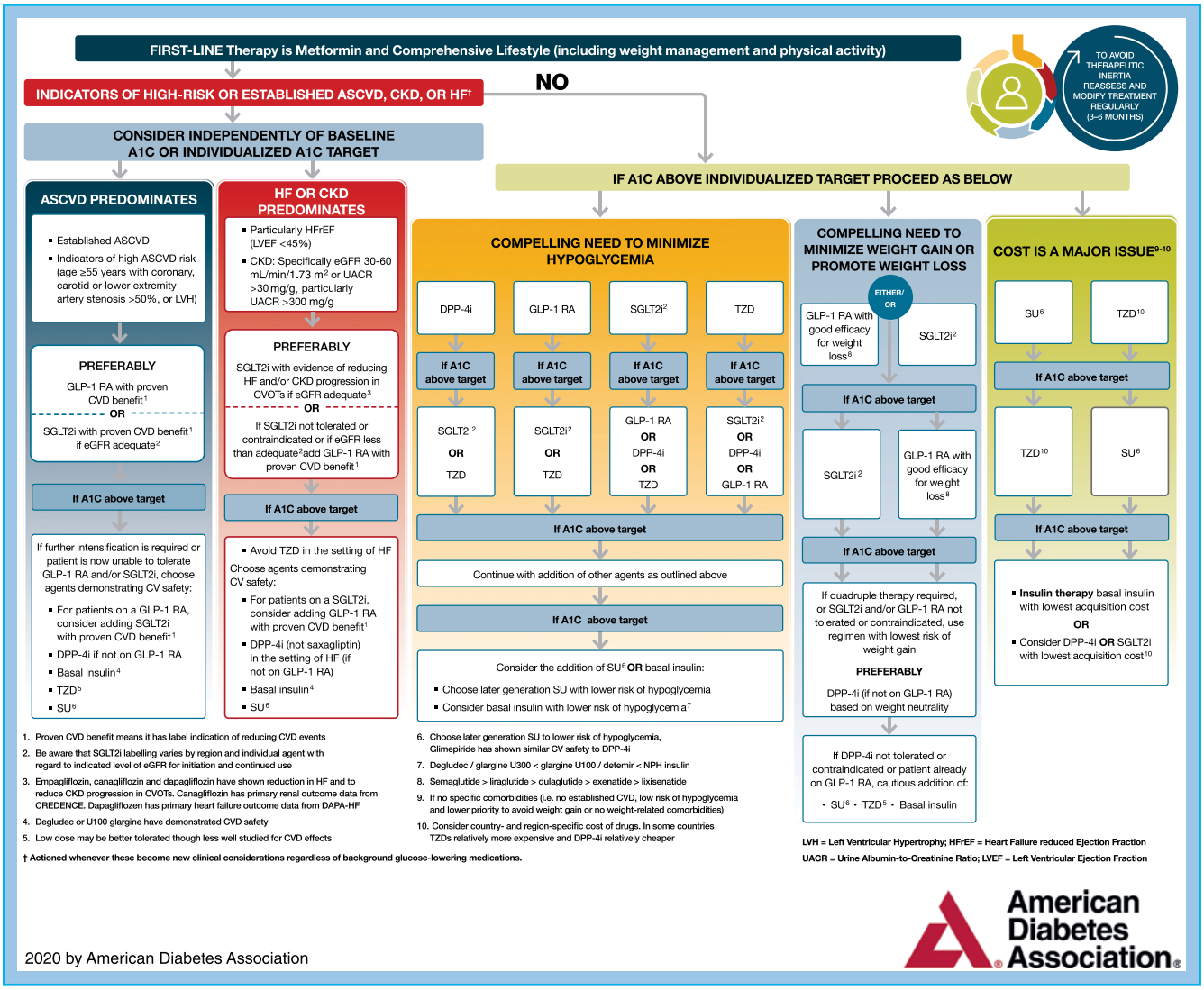

Figure 25.3 European Association for the Study of Diabetes (EASD)/American Diabetes Association (ADA) approach to management of hyperglycaemia. Source: Buse et al. (2020) [34].

A common limiting factor in the ability to achieve optimal glycaemic levels is hypoglycaemia, which is one of the most unpleasant, socially aversive, inconvenient, and feared side effects of diabetes medication (Chapter 40). The frequency and severity of hypoglycaemic episodes should be discussed. An exploration of the underlying causes and advice about prevention are required for the future.

When a person with diabetes is treated with insulin, it is important to ensure that they carry a readily accessible source of fast-acting glucose, such as glucose tablets. Concentrated glucose solution and glucagon should also be made available for use in more severe hypoglycaemia. As these treatments may only be used infrequently, it is worth regularly checking whether they are in date. Furthermore, as they need to be administered by a third party, it is important to ensure that the friends and relatives of the person with diabetes know how to administer them and are confident in doing so before they are needed.

In some instances, the only way of avoiding disabling hypoglycaemia is to accept a higher HbA_{1c}. This recalibration of glycaemic goals should be decided with the individual and a target appropriate for the circumstances should be agreed. As well as the risk of hypoglycaemia, other factors should be considered when discussing the target, including the overall clinical situation and risk of complications affecting the individual.

Assessment of cardiovascular risk

For many years, the commonest cause of death in people with diabetes was cardiovascular disease and much effort has been expended to develop strategies that will reduce its morbidity and mortality [38].

Cardiovascular risk should be assessed at least once a year for people with diabetes. This should include a history of cardiovascular risk factors, such as family history and smoking, an examination to include weight, waist circumference, and blood pressure, as well as investigations such as a lipid profile. The results of this assessment can be used to calculate cardiovascular risk using the various risk engines available. Some, such as the UKPDS risk engines for coronary heart disease and stroke, were designed specifically for use in people with diabetes and are readily available on the internet [39,40].

Diabetes is a major risk factor for cardiovascular disease [41]. This has influenced prescribing guidelines, which now recommend that specific pharmacological interventions are required to reduce

the incidence of cardiovascular disease in people with diabetes regardless of risk assessment. Large randomized controlled trials have shown the effectiveness of these interventions and are discussed in greater detail in Part 8 [42].

Although physicians may appreciate the close connection between diabetes and cardiovascular disease, many people with diabetes have never been told about this increased risk and the importance of blood pressure and lipid control. Thus, many individuals are not taking appropriate drugs for cardiovascular prevention, or if they are the doses may be inadequate to achieve recommended targets. When working with someone with diabetes, it is important that strategies to reduce cardiovascular disease and the need for preventive drugs are discussed. In addition, the increased vascular damage promoted by smoking in the setting of diabetes may not be appreciated.

The main classes of drugs used are lipid-lowering drugs, predominantly statins, and antihypertensives, particularly drugs acting on the renin–angiotensin system. Antihypertensives are also important in the prevention of microvascular complications, as discussed in the following section. Specific guidance about blood glucose–lowering agents recommends the use of human glucagon-like peptide-1 (GLP-1) receptor agonists and sodium glucose cotransporter 2 (SGLT-2) inhibitors because of the cardiovascular benefits observed in clinical trials of these agents.

While each individual intervention for the various risk factors is important in the prevention of macrovascular disease, the Steno 2 trial has demonstrated that a coordinated approach to the management of cardiovascular risk can be successful [6]. In this study, the clinic setting and protocol-driven approach to overall cardiovascular risk led to significantly improved mortality compared with routine care.

Microvascular complications

With time, most people with diabetes will have develop microvascular complications [43]. Many complications will remain asymptomatic until they have catastrophic consequences. The management of microvascular complications involves measures to prevent, detect, and treat. General measures, such as optimal glycaemic and blood pressure management, lead to a reduction in the incidence and progression of microvascular complications, but specific preventive measures are also needed and are discussed next [3–5, 44].

Eyes

Globally diabetic retinopathy remains the commonest cause of blindness in people of working age (Chapter 43). It is almost invariably asymptomatic until there is a catastrophic sight-threatening haemorrhage. For this reason, it is important to screen regularly for retinopathy to allow treatment before haemorrhage and visual loss occur. Traditionally this has been performed by examination of the visual acuity and fundoscopy within the diabetes clinic at least on an annual basis, although longer screening frequencies are being considered. Alternatively, in many countries dilated ophthalmological examinations are regularly performed by a specialist.

The gold standard for screening now, however, is digital retinal photography, which may be undertaken in several different settings. When this is performed outside the traditional diabetes clinic, communication between the screener and diabetes team is essential if other aspects of diabetes care are to take account of the development of retinopathy.

Where retinopathy is detected within the clinic, it is the responsibility of the clinic to ensure that the individual is referred for specialist ophthalmological attention in a timely fashion.

Neuropathy

Distal symmetrical polyneuropathy is the commonest form of neuropathy in diabetes and is addressed in the following section on the diabetic foot. Autonomic neuropathy may affect the person with diabetes in several ways, for example gustatory sweating, postural hypotension, or bloating (Chapter 45). Healthcare professionals should be alert to this possibility if symptoms suggestive of these conditions are raised.

Foot problems

Diabetes is the commonest cause of non-traumatic lower-limb amputation in high-income countries (Chapter 53). Around 10–15% of people with diabetes develop a foot ulcer as a result of the combination of peripheral neuropathy and vascular insufficiency to the foot.

Prevention of ulceration is an important goal and requires educating the person with diabetes so that they are aware of this possibility. It is important to inform people that they should not delay obtaining professional help if problems ensue.

An assessment of the risk of foot ulceration is needed at least annually and more frequently when neuropathy or vascular disease is present. The assessment should include a history of previous ulceration and trauma, as well as an examination of the skin, vascular supply, and sensation. Opportunistic foot screening should also be performed if an individual with diabetes is admitted to hospital.

In people with numbness, close attention to discovering unsuspected foot lesions, including examination of the sole of the foot using a small mirror, must be performed by the individual on a regular basis. This can lead to rapid intervention and prevent an early infection from progressing, potentially averting such devastating consequences as osteomyelitis and gangrene.

Prompt referral to the podiatrist and foot clinic should be arranged by the diabetes clinic if needed.

Kidneys

Diabetic nephropathy is characterized by a progressive increase in urinary albumin excretion that is accompanied by increasing blood pressure and decline in glomerular filtration rate, ultimately culminating in end-stage renal disease (Chapter 44). It is also associated with a marked increase in the rate of cardiovascular disease.

Microalbuminuria, the earliest stage of nephropathy, affects around 50% of people with diabetes after 30 years, while frank proteinuria affects a quarter of people with type 1 diabetes after 25 years. Diabetic nephropathy is a common reason for the initiation of renal replacement therapy. Although it appears that with modern treatments of diabetes the risk of an individual with diabetes developing end-stage renal disease is falling, the absolute numbers requiring renal replacement therapy are increasing in line with the increased prevalence of diabetes worldwide.

Diabetic nephropathy is asymptomatic and so screening is required annually. This is usually achieved by measurement of urinary albumin excretion (UAE). The commonest method is a single urinary albumin-to-creatinine ratio (ACR) measurement, which should be repeated two to three times if abnormal. An estimation of glomerular filtration rate should be obtained annually.

The primary prevention of nephropathy relies on excellent glycaemic management as well as tight blood pressure control. Once nephropathy is present, blood pressure management is the mainstay, as there is little evidence that glycaemic management at this stage slows the rate of progression. The antihypertensive drugs of choice are angiotensin-converting enzyme (ACE) inhibitors

or angiotensin-2 (AT-2) receptor antagonists, as they have specific effects on renal blood flow [45,46]. SGLT-2 inhibitors also reduce the progression of nephropathy, independently to their effect on glucose.

It is important that the person with diabetes understands the need for screening followed by treatment if nephropathy develops. Timely referral to the nephrology team is needed to ensure that the management of renal disease is undertaken promptly in those with abnormal renal function.

Diabetes emergencies

Diabetic ketoacidosis and hyperosmolar hyperglycaemic syndrome

Diabetic ketoacidosis and hyperosmolar hyperglycaemic syndrome are potentially life-threatening emergencies (Chapter 41). The person with diabetes needs to be educated about the risk of these and strategies to prevent them from happening should be discussed. If a person with diabetes has been admitted with diabetic ketoacidosis or hyperosmolar hyperglycaemic syndrome, the opportunity should be taken to explore the reasons why this episode occurred and to identify what might be changed to prevent it from happening in future. The commonest causes of hyperglycaemic emergencies in those with pre-existing diabetes are infections and insulin omission and errors. Bolus calculators are increasingly commonly used; however, it is crucial to regularly check that set parameters remain accurate, including insulin-to-carbohydrate ratio and insulin action time (sometimes called insulin on board, IOB), to ensure that the correct amount of insulin is being advised and delivered. It is particularly important that people with diabetes also understand the 'sick-day' rules, where insulin should never be discontinued and indeed doses may need to be increased even when appetite is diminished.

Hypoglycaemia

Hypoglycaemia is a common diabetic emergency affecting most people with type 2 diabetes and ~60% of insulin-treated people with type 2 diabetes (Chapter 40). Hypoglycaemia may have a major adverse effect on quality of life and fear of hypoglycaemia is the most important limiting factor in the achievement of optimal glycaemic levels.

It is important that the person with diabetes is educated about the symptoms of hypoglycaemia and the actions to be taken to prevent and treat it. As noted earlier, friends and family members should be invited to learn about hypoglycaemia and its management in order to intervene when necessary, for example by providing glucagon treatment if the person with diabetes is unconscious. If hypoglycaemia becomes disabling or recurrent, it is important to explore underlying causes (Table 25.2).

Table 25.2 Causes of hypoglycaemia.

- Excessive insulin administration
  - Person with diabetes, doctor, or pharmacist error
  - Deliberate overdose during a suicide or parasuicide attempt
- Excessive sulfonylurea administration
- Unpredictable insulin absorption
  - Insulin is absorbed more rapidly from the abdomen
  - Lipohypertophy
- Altered clearance of insulin
  - Decreased insulin clearance in renal failure
- Decreased insulin requirement
  - Missed, small, or delayed meals
  - Alcohol
    - Inhibits hepatic glucose output
  - Vomiting
    - May occur with gastroparesis, a long-term complication of diabetes
  - Exercise
    - Promotes glucose uptake into muscle
    - Increases rate of insulin absorption
- Recurrent hypoglycaemia and unawareness

Lifestyle issues

Diabetes has social, psychological, and medical consequences and an important aspect of diabetes care is to discuss how diabetes may be affecting social issues such as driving, education, and employment (Chapter 66). The healthcare professional may need to act as an advocate for the person experiencing discrimination. Some aspects of lifestyle also affect diabetes care, such as diet, exercise, smoking, and alcohol. These issues should be discussed sensitively in order help the person with diabetes understand how their lifestyle affects their diabetes and general health. Support should be given to help and encourage the individual to make changes to their lifestyle where these are appropriate. Psychological support should be offered where necessary.

Psychological issues

Both the diagnosis of diabetes and the chronicity of the condition can provoke a number of psychological reactions, such as anger and sadness in the individual that may be akin to a bereavement reaction or a chronic sorrow response (Chapter 63). More serious mental health problems, such as depression, are common in people with diabetes and these can impede the person's ability to achieve optimal glycaemic management [47] (Chapter 65).

It is important for those working in diabetes care to explore with the individual whether they are experiencing psychological problems, as they may be reluctant to raise this in the consultation. While all members of the diabetes team should be able to recognize and address basic psychological problems, an essential team member is a psychologist who can address more complex needs. Despite the importance of psychological issues, this need is frequently unmet because of a lack of trained healthcare professionals.

The Diabetes Attitudes Wishes and Needs (DAWN™) study, a global survey of people with diabetes and healthcare professionals involved in their care, substantiated the association of diabetes with multiple psychological challenges and the close interrelationship between emotional well-being and diabetes outcome [48]. It also pointed to important deficiencies in the emotional care of and support for people with diabetes, which became the basis for the DAWN Call to Action with the goal of implementing person-centred diabetes care.

In 2012, the second global DAWN study (DAWN2™) was conducted to re-evaluate the state of diabetes care, both globally and within each of the 17 participating countries. In the global DAWN2 study, nearly half of the surveyed people with diabetes reported diabetes-related distress, 12% rated their overall quality of life 'poor' or 'very poor', and approximately 14% had likely depression [49]. Notably, family members were also considerably affected by having an adult with diabetes in their household, with 35% experiencing the care for the person with diabetes as a burden [29]. In 45% of family members, diabetes care had its most negative impact on emotional well-being [29].

Sexual health

Sexual dysfunction

Sexual dysfunction is more common in both men and women with diabetes than in the general population (Chapter 54). This can affect the person's quality of life considerably [50, 51]. Many people are reluctant to discuss this aspect of their lives because of embarrassment, and so it is the responsibility of the healthcare professional to enquire about this. There are now effective treatments for erectile dysfunction and failure to ask about this can deny the person with diabetes the opportunity to receive this treatment.

Pregnancy planning

Starting a family is an important milestone for many and the presence of diabetes can make this decision more difficult for women with diabetes (Chapter 71). Women are often worried about the effects that diabetes will have on their pregnancy and vice versa. The implications for the long-term risk of diabetes in the offspring are also of concern.

Planning for a pregnancy by a woman with diabetes can dramatically improve the outcome, reducing the risk of miscarriage, congenital malformations and macrosomia, with its attendant risks of shoulder dystocia, and neonatal hypoglycaemia [52]. Most oral medications should not be used in pregnancy and the treatment regimen may need to be altered as part of the planning process.

Despite this, many women enter pregnancy without adequate preparation or pre-conception care. It is therefore incumbent on the healthcare professional to discuss pregnancy with all women of child-bearing age, including adolescents, to ascertain their plans regarding pregnancy. The answers are often not black and white; women may not actively be planning to become pregnant, but are sexually active and not using effective contraception. Contraceptive advice is needed and where a pregnancy is being planned, women should be referred to a dedicated pre-conception clinic, as these have been shown to improve the outcomes of diabetic pregnancies.

With an increasing number of women with type 2 diabetes of child-bearing age, it is important that pre-conception advice is not solely focused on those with type 1 diabetes. This is particularly relevant because many women with type 2 diabetes are not seen in specialist centres.

Prompt referral to a joint diabetes antenatal clinic is necessary once a woman becomes pregnant.

Men may also have concerns about embarking on a family because of the increased risks of diabetes in their offspring and these anxieties need to be discussed sensitively.

Inpatient diabetes care

It is estimated that around 10–15% of people in hospital have diabetes (Chapter 39). In many instances the diabetes is coincidental to the admission and the individual remains capable of managing their own diabetes, often with greater skill than the healthcare professionals around them. Optimal diabetes management remains an important goal, as this improves the rate of recovery and may lead to an earlier discharge.

Admission to hospital is a worrying time, but much of the fear can be alleviated if a full explanation of the treatment in hospital is given along with an opportunity to discuss any particular concerns. Being given the opportunity to discuss the management of diabetes can be reassuring. Where possible, the person with diabetes should be allowed to continue to self-manage their diabetes. The individual should be encouraged to bring in their own insulin supplies where admissions are planned. There should be access to their regular diabetes healthcare team where possible, as the admission may provide an occasion to check techniques and results. Ready access to carbohydrate and appropriate coordination of mealtimes, snacks, and medication should obviate the need for more dramatic treatment of hypoglycaemia.

There will be times when the person with diabetes is unable to manage their diabetes themselves. In these instances, the responsibility will fall entirely on the healthcare team, for example during surgery when the person with diabetes is unconscious and requires intravenous insulin and dextrose.

Following discharge, clear communication with the primary care and hospital diabetes teams is essential so that any changes in management or medication are made known to those involved in the individual's care.

Involving people with diabetes in the planning of healthcare and service development

Involving people with diabetes and their carers in the planning and decision making of local health services enables these to be built around the needs of those who use the service, rather than the needs of the system [53]. An open dialogue is needed, and service users should feel that their views are listened to. This will improve the accountability for and legitimacy of any decisions made and is likely to ameliorate clinical and care outcomes. People with diabetes should be encouraged to express their views and concerns about their services, as better feedback about service provision should help to improve and shape future provision of care.

Conclusion

The aim of diabetes care is to improve the lives of those with diabetes. This can only be achieved through a partnership between the person with diabetes and a multifunctional healthcare team that should be in place to support the person with diabetes.

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26 Education to Empower the Person with Diabetes

Ingrid Willaing[1] and Michael Vallis[2]

[1] Steno Diabetes Center Copenhagen, Copenhagen, Denmark, and Department of Health Services Research, Institute of Public Health, University of Copenhagen, Copenhagen, Denmark

[2] Department of Family Medicine, Dalhousie University, Halifax, NS, Canada

Key points

- Diabetes education and psychosocial support are critical elements of care for all people with diabetes and their family members.
- Being able to self-manage diabetes requires substantial knowledge, motivation, and behavioural competencies on the part of people with diabetes and their family members.
- Diabetes education needs to be implemented in a sufficiently flexible manner to be incorporated into multiple settings, not just formal and structured diabetes education.
- People with diabetes must be placed at the centre at all times in diabetes education. Active involvement in their own healthcare must be prioritized over educator-dominated involvement.
- Diabetes education programmes are more effective if they are based on participant- and empowerment-oriented principles and principles of adult learning.
- Group-based diabetes education has a positive effect on clinical outcomes, health behaviours, and psychosocial outcomes, including glycated haemoglobin (HbA_{1c}), fasting blood glucose concentration, diabetes knowledge, self-management, empowerment, and self-efficacy.
- The provision of appropriate training of diabetes educators, including the management of psychosocial issues, cannot be overestimated.
- Group processes and active participation during diabetes education appear to be more important for improving coping skills than the didactic content of the programme.
- People with diabetes should be supported to work specifically and realistically with setting goals and to think about potential obstacles and facilitators to achieving them.
- Family-based diabetes education interventions seem to be a potentially important supplement to enhance diabetes management in everyday life.
- Evaluation of diabetes education should focus on understanding how, for whom, and under what conditions specific programmes will work.
- The main limiting factor of diabetes education is that it almost always does not include ongoing care and education.

The foundation of diabetes self-management education and support

There is broad consensus in the global diabetes community that diabetes education and psychosocial support are critical elements of care for all people with diabetes and their family members [1]. Yet questions remain about the extent to which diabetes education effectively enhances self-management or addresses the psychosocial aspects of living with diabetes. The purpose of this chapter is to support enhanced competency in the delivery of self-management education and psychosocial support by clearly specifying the values, attitudes, and competencies that promote self-management.

Many issues that impair the efforts of diabetes educators in promoting self-management are grounded in communication challenges [2]. Educators unwittingly restrict participation from people with diabetes through time constraints, pre-planned topics, and persuasive recommendations [3] that operate counter to the evidence that goals generated by people with diabetes produce better outcomes than goals generated by healthcare professionals [4]. It makes sense that a person will be more committed to pursuing their own goals than goals that are *given* to them by another person. A health technology assessment of education programmes concluded that those for people with diabetes are more effective if they are based on participant- and empowerment-oriented principles and principles of adult learning [5]. The best outcomes of patient education seem to be produced with an empowerment approach, which is problem based, and individually and culturally tailored to address psychosocial, behavioural, and clinical issues relevant to people's needs and readiness to learn [6]. In reality, educators are responsible for translating abstract concepts and theories into concrete programmes tailored to the needs of different individuals with diabetes [7].

Diabetes education and support has the potential to empower people with diabetes to live well with diabetes. For the individuals with diabetes and their family, this means the freedom to live as they want while feeling healthy and being safe. For people with diabetes and their healthcare team, this also means achieving

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desirable clinical outcomes such as glycaemic, blood pressure, and cholesterol targets [8–10].

Diabetes self-management education and support (DSMES) is an ongoing process to provide the individual with the knowledge, skills, and confidence to self-manage [11,12]. DSMES is intended to support informed decision making, problem solving, health behaviour change, and active collaboration with a healthcare team. The process of DSMES must be based on the needs, goals, and life experiences of the person with diabetes. As such, it is less about teaching and more about collaborating.

Modalities of education

There are many evidence-based curricula available for diabetes education. The UK National Institute for Health and Care Excellence (NICE) defines structured diabetes patient education as 'A planned and graded programme that is comprehensive in scope, flexible in content, responsive to an individual's clinical and psychological needs, and adaptable to his or her educational and cultural background' [13]. In its review of the evidence, NICE identifies principles of good practice, including the following [14]:

- It is evidence based and suits the needs of the person.
- It has specific aims and learning objectives and supports the person and their family members and carers in developing attitudes, beliefs, knowledge, and skills to self-manage diabetes.
- It has a structured curriculum that is theory driven, evidence based, and resource effective, has supporting materials, and is written down.
- It is delivered by trained educators, who have an understanding of educational theory appropriate to the age and needs of the person, and who are trained and competent to deliver the principles and content of the programme.
- It is quality assured, and reviewed by trained, competent, independent assessors who measure it against criteria that ensure consistency.
- The outcomes are audited regularly.

There are many programmes and methods available for diabetes education and support, with more or less evidence of effect (e.g. [15–17]). There is evidence for the effect of one-on-one education as well as group education [18]. Group-based education can be cost-effective and equally or more satisfying to recipients [6,19,20]. Group-based education including peer support has the advantage of observational learning and modelling [21,22], which may be at least as important for improving coping skills as the didactic content of the programme [23,24].

Individual differences and contextual factors are critical to success in diabetes education. Support is likely to be especially beneficial in relation to specific events in life such as being diagnosed in adulthood [9,25], starting to use diabetes technology, a wish to participate in extreme physical activity such as a marathon [26], the Covid-19 pandemic [27,28], or other new situations in the lifespan generating specific needs [29,30]. Given that at least half of people with diabetes do not participate in formal diabetes education services [31], DSMES needs to be adapted to settings beyond formal diabetes education services such as primary or specialty care, community settings, and public health [32]. DSMES is based on three main building blocks: values, tools, and competencies. This chapter is structured around these three areas, which will be described in more detail in what follows.

Values, competencies, and tools

Diabetes is managed on a daily basis by the person with diabetes in the context of their sociocultural environment [33,34]. It is critical to accept that diabetes is not a goal sought by the individual: no one chooses to have diabetes. It is an unwanted intrusion into a person's life that is a major source of threat and burden. The implication of this is that it can be expected that the person with diabetes would want to minimize the intrusiveness of the disease in their life. The irony is that self-management requires significant vigilance and effortful health behaviours, which increase psychological intrusion. Successful self-management support can help the individual to psychologically reframe diabetes self-management from an intrusive burden, which impairs quality of life, to a chosen strategy that enhances quality of life; that is, as empowerment. In this way, DSMES is inseparable from managing the emotional and psychosocial aspects of living with diabetes. DSMES must facilitate this fundamental psychological reframing, which is an internal process of the person with diabetes and not controlled but supported by the healthcare team.

Accepting that diabetes is a self-managed disease that no one chooses to have and that requires considerable, continuous, and arduous self-care behaviours places the educator in the proper context. The power in the relationship does not belong to the educator, but to the individual. Thus, tools and procedures should not be prioritized over the person with diabetes and the healthcare professional relationship. Rather, tools should be used to empower the person with diabetes and enhance the collaboration between the person with diabetes and the healthcare team. Diabetes self-management occurs outside of the clinical encounter where the individual is in charge of their choices. To make the most of DSMES, the educator needs to implement an evidence-based care plan. However, this plan should not prioritize tools and procedures over the use of the patient–healthcare professional relationship to empower the person with diabetes to *choose* to follow recommended procedures and tools. As such, the foundation of DSMES is more value based than tool based. This is illustrated in Figure 26.1, where values are the bedrock that define the competencies needed to facilitate self-management.

The value of DSMES includes respecting the *autonomy* of the individual (their questions are most important to address, and their decisions carry the greatest weight) by *collaborating* (being person

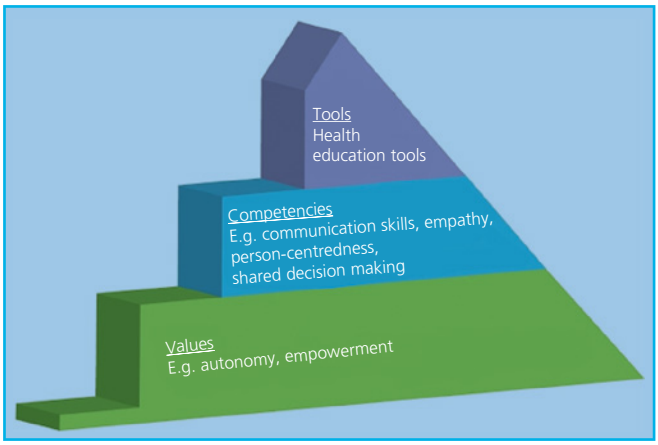

Figure 26.1 Values, competencies, and tools in diabetes education and support. Source: Hansen et al. 2018 [35].

centred and using shared decision making) to achieve *empowerment*. Healthcare professional competencies and the use of relevant tools should be perceived as a stepwise execution of these values. In fact, value-based education and support by competent educators may obviate the need for tools. A meta-analysis of motivational interviewing discovered that manual-based implementations were less effective than implementations that were not manual based, but instead based on the 'spirit of motivational interviewing' [36].

Organizing the activities of the educator around the concepts of person-centredness, collaboration (shared decision making), and empowerment represents a major shift towards placing the relationship in front of education [34, 37]. It is unacceptable for a diabetes healthcare professional to say 'I did not have time to address the psychosocial aspects of diabetes'. Many diabetes educators are more comfortable with providing recommendations and teaching management skills than with addressing the psychosocial context of a person's life [38, 39]. This raises a stressful situation for the educator; that is, issues unrelated to diabetes may be overriding priorities for the person with diabetes, limiting the goals and expectations of the educator at any moment in time. Educators experience numerous barriers regarding the facilitation of person-centred and participant-involving education [39, 40], despite the evidence in favour of these experiences [41]. Thus, DSMES should be standardized by function, not by content [39, 40, 42]. Traditional education focuses on input (what healthcare professionals present to the patient). We are claiming that output is more important (what is important for the person with diabetes to do or to hear about).

The role of the healthcare professional: how do we guide people with diabetes to self-management behaviours?

Person-centred DSMES is intended to empower people with diabetes to engage in the challenging behaviours associated with managing glycaemic, lipid, and blood pressure levels and prevention of complications. For many individuals, this means becoming motivated and skilled to engage and sustain behaviours that are challenging to maintain. For healthcare professionals, this requires shifting from being an educator to being a collaborator first and an educator second [2, 39, 40, 43]. Preechasuk et al. reported a broad survey of diabetes educators, doctors, and administrators in Thailand regarding diabetes self-management education [44]. Only 30% of educators reported that self-management education was effective, with obstacles to care including time, behaviour change skills for the healthcare professional, and perceived lack of interest and motivation for the person with diabetes. Clearly, universal uptake of DSMES is lacking. Based on the values of autonomy, collaboration, and empowerment, the competencies of the diabetes educator are in the ability to establish a change-based relationship with the person with diabetes. As such, it is the roles that the educator takes in the relationship that define DSMES competencies. Effective change-based relationships will promote behaviour change interventions that can be supported by tools.

The fundamental relationship dynamic that will promote DSMES involves the educator basing their relationship on dialogue and participation.

Dialogue, as a way of conducting diabetes education [45, 46], differs from the traditional one-way didactic model: the monologue. Didactic education can successfully convey information, but it is less successful in supporting individuals with diabetes to take responsibility for self-management [5]. Much diabetes education does not engage the person with diabetes [47]. Behaviour change theory indicates that educators should elicit commitment, identify challenges, set goals, increase self-efficacy, and address barriers to change, and the main way to do this is through dialogue [48, 49]. It is useful to take the position that behaviour change is hard, and sustained behaviour change is even harder. Once behavioural habits become entrenched, much behaviour is cued by the environment, as well as natural preferences. For example, a 55-year-old man with type 2 diabetes who has never liked exercise and dislikes the idea of medication and being labelled as ill (preferences), and who has developed unhealthy eating and drinking habits as part of a stable and supportive friendship circle (cued environment), is unlikely to change behaviour as a result of listening to lectures on the benefits of healthy eating, taking medication as prescribed, and physical activity.

Participation likewise implies a shift in perspective from a disease- and expert-centred approach towards the needs of the person with diabetes. Effective and meaningful diabetes education requires that people with diabetes are actively involved and that teaching is tailored to their needs and preferences [45, 50, 51]. One way of conceptualizing this is as in a journey. The educator might make the first step, in the form of a recommendation or educational intervention, but then needs to see if the individual is able to follow that step. Traditional education involves the educator conveying huge amounts of information, effectively leaving the person with diabetes far behind as more and more knowledge and recommendations are conveyed. Evidence on the value of the teach-back method (having the individual summarize their learning throughout the encounter and not moving on till the person with diabetes has understood the message) in chronic disease management supports this notion of participation [52]. A useful concept here is *talk time*: monitoring who is talking more in an encounter ensures that the person with diabetes has enough time to express themselves fully [53, 54].

Educator knowledge, attitudes, wishes, and needs must take second place to the decisional processes of the person with diabetes. Consider the same 55-year-old man with diabetes who dislikes exercise, has never been physically active, and has many individual, social, and financial barriers to increasing activity. What are the conditions under which this person will choose to do all the work necessary to add a disliked behaviour to his routine? Overcoming the personal barriers to change is less likely to arise from teaching and telling than it would from effective understanding and supportive negotiation of health behaviour choices (participation through dialogue). In this example, the educator could communicate understanding and respect of the challenges to the recommended behaviour, and explicitly acknowledge that the person is in charge of the decision, while seeking permission to discuss ways to overcome barriers, be they informational, motivational, emotional, relational, or practical. The AADE7 Self-Care Behaviors framework [55] recommends orienting services around the behaviours of healthy eating, being active, glucose monitoring, medication taking, problem solving, reducing risk, and healthy coping. However, many educators will need to change their approach in order for self-management support to be implemented effectively. Involvement through dialogue requires the person–healthcare professional relationship to be one in which the patient feels comfortable sharing their truth without judgement by the healthcare professional. The majority of people with chronic illness avoid telling their clinician

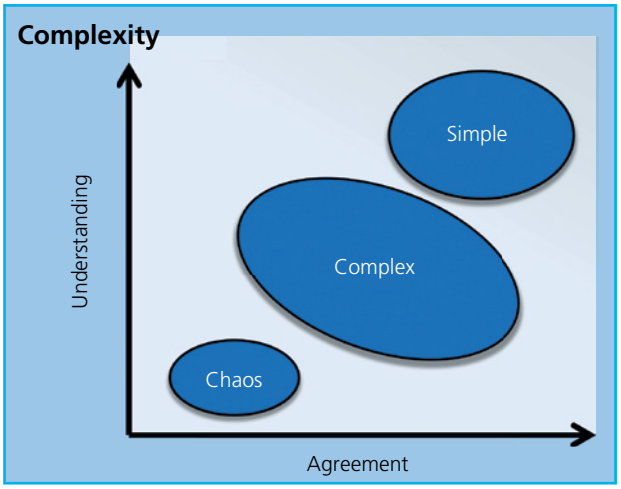

Figure 26.2 Complexity, understanding, and agreement.

important information and non-disclosure is based primarily on fear of judgement by healthcare professionals [56].

Many educators have developed the belief that their professional role is to provide the person with diabetes with the knowledge and skills they believe are needed to perform the recommended behaviours. They are the expert and it is their responsibility to educate. This relationship dynamic has been described as the 'expert clinician with the uninformed help-seeker' and can be understood through an appreciation of complexity (Figure 26.2) [57]. Some constructs, functions, or domains are simple, some are complex, and some are chaotic. This distinction can be understood by considering the degree of understanding and the degree of agreement regarding a phenomenon [57].

When the degree of understanding about a phenomenon is high and the degree of agreement on how to address the phenomenon is high, this is an indication of a simple system and a situation where reductionist protocols are effective. Since most medical professions base their training on the scientific method that emphasizes reductionism (determining the diagnosis) and determinism (understanding the mechanism of action), it naturally follows that this is a default relationship position an educator takes. However, not all systems are simple. When the degree of understanding and the degree of agreement are low, this is called a chaotic system; there is no precise guidance available. In this situation, gathering and organizing information to gain understanding is most effective (pattern recognition or phenotyping). When degrees of understanding and agreement are partial, this is called a complex system. Behaviour, including diabetes self-management behaviour, can be considered to be at least complex. As such, appropriate interventions are not so much guided by procedure but by principle. Different procedures may be equally appropriate if they have similar impacts on the principle. For example, if self-efficacy is the principle that predicts sustained behaviour, then any procedure recommended by an educator that increases self-efficacy is acceptable.

Effective self-management support shifts the professional role from method (what one does) to principle (the guiding rationale for what one does). Given that self-management necessarily places the responsibility on the person with diabetes, it becomes necessary to respect the choices made by the person. If the educator focuses on the principle, then they can negotiate the method without threatening personal choice.

Reflecting on the dominance of the scientific method in healthcare, it is no surprise that educators often do most of the talking in clinical encounters, that they make frequent recommendations in the form of statements, and that they commonly interrupt individuals with diabetes if they stray from the agenda of the educator [58]. These relational dynamics reflect the educator as expert, where professional competency is based on conducting an assessment to make a diagnosis, determining a treatment intervention based on evidence, and evaluating how well the person responds to the intervention. This professional competency model of diagnose, determine treatment, and measure outcomes works well if the outcomes being achieved are under the direct control of the clinician. When outcomes are not determined by the competency of the clinician but by the behavioural choices made by the person with diabetes outside of the clinician encounter, these competency standards no longer apply. Dialogue and participation explicitly reframe this dynamic from *teach and tell* (educate and recommend) to a shared interaction. Figure 26.3 shows how competency can be reframed using the concepts of dialogue and participation. The left-hand panel in Figure 26.3 shows the traditional model where outcomes, which are based on the clinician's expertise, follow from the diagnosis, treatment, and focus on outcomes [38]. In simple biomedical contexts, this is fine. In behavioural and sociocultural contexts, the task of diagnosing can be replaced with the task of describing. It is not the clinician's job to tell the person what their problem is, but it is the clinician's job to understand the patient's behaviour. For instance, medication taking or vaccinations can be understood by examining the person's beliefs regarding perceived need for treatment and perceived concerns about treatment. Once behaviour is understood, it is the job of the clinician to help the person with diabetes appreciate the predicted outcome of their current behavioural choices. Rather than judging the outcomes of the person's efforts, the clinician must link important (to the person) outcomes to the choices made and encourage different choices consistent with recommendations. So, using dialogue to engage the person in a participatory approach can improve self-management via the skills of description, prediction, and choice – not diagnosis, treatment determination, and outcome judgement (Figure 26.3).

Working with dialogue and participation

Dialogue and participation enable the educator to shift from the expert (teach and tell) to collaboration (collaboration and empowerment). In doing so educators manage different roles and the shifting between roles; the juggling is, however, challenging [59]. Juggling is the ability to master switching between different roles to meet the needs of the individual or group and to evoke readiness to change [46]. Some well-recognized juggler attributes are:

- *Humility* – the ability to be approachable without projecting one's self and beliefs onto the group.
- *Flexibility* – openness to try new process approaches, willingness to change, or stretch outside one's boundaries in the facilitator role.
- *Professionalism* – being ready to deal professionally with feelings in the group [60].

The roles that are juggled include the embracer, the facilitator, the translator, and the initiator [46, 61].

The *embracer* role is based on empathy [62, 63], which encompasses the desire and ability to understand people with diabetes on their own terms [62]. Morse et al. [64] propose a descriptive model of clinical empathy with affective, moral, cognitive, and behavioural dimensions. Norfolk et al. [62] propose a model about the empathic

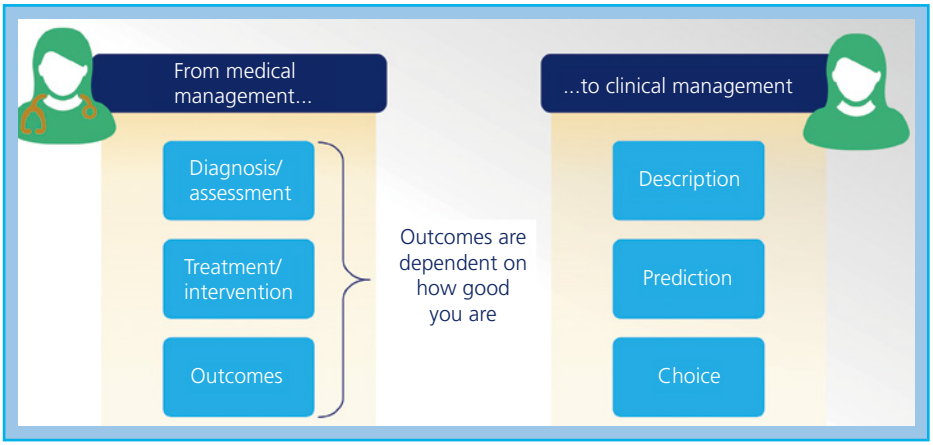

Figure 26.3 Are behavioural interventions doomed to fail? Source: Vallis 2018 [38].

journey towards therapeutic rapport in consultations focusing on the doctor's behaviour, motivation, and required skills. The factors mentioned in these studies are important competencies for educators' ability to act in the embracer role.

The *facilitator* role is rarely described in the literature. Notable exceptions are guidelines for facilitating patient empowerment programmes [65] and a study about speech practices facilitating patient participation in health counselling, in which concrete facilitation skills are suggested [3]. However, other professional fields, such as business and organization, provide more extensive literature on facilitation [60, 66].

The *translator* role, in which the educator translates medical concepts into relevant and understandable information, implies a change of the typical health educator roles. In traditional medical and disease-specific patient education, educators give information and advice, handle acute situations, and perform problem solving [63]. Following patient demands for a more active role in healthcare, the Ottawa Charter emphasized the need to view the individual as a *whole person* [67]. As translators, healthcare professionals recognize that they are experts in medical knowledge and that individuals with diabetes are experts on their lives [68].

The *initiator* role closely links to principles of motivational interviewing [69] and empowerment interventions [70]. The initiator faces the challenge of avoiding confrontation or authority traps such as *knowing best*. In general, facilitation and participatory methods are rarely part of the healthcare professional curriculum [63], which may explain the challenges experienced when delivering participatory, group-based diabetes education.

The tool in Figure 26.4 to self-assess professional skills in facilitating group-based diabetes education seems useful and stimulating, and is suggested as an excellent starting point to promote more person-centred communication between individuals with diabetes and healthcare professionals [71]. It is easier for healthcare professionals to embrace the roles of translator and embracer than those of facilitator and initiator [72].

A framework to guide selection of education methods

Juggling the roles of embracer, facilitator, translator, and initiator using dialogue and participation defines many of the competencies needed for effective DSMES. In addition, the educator is required to develop competency in eliciting behaviour change. One of the learnings from behavioural sciences is the importance of theory-driven interventions. Behavioural theories explain why people engage in certain behaviours and provide a guide to promote behaviour change. By contrast, the use of tools, without theory, might be misguided. Theory can guide the selection of which tool is useful in a given situation. For instance, the literature supports regular weighing as a way of maintaining a healthy weight. However, regular weighing may be negative for one person and positive for another. If a person feels disappointed and shameful when the weight on the scale is not what was hoped for, regular weighing may be demotivating rather than motivating.

At the centre, the person with diabetes is an individual who will make specific behavioural choices (person as decision maker). A dominant theoretical model describing how people make behavioural choices is the Self-Regulation Model, also referred to as the Health Belief Model [73]. There are five dimensions of illness beliefs:

- Consequences (e.g. perceived seriousness)
- Personal control
- Treatment control
- Timeline
- Emotional representation.

Understanding these beliefs can be a valuable guide to the diabetes educator for supporting the person with diabetes. Consider the person who perceives the consequences of their diagnosis as minor (low seriousness) or someone who does not believe that treatment will reduce complications, perhaps based on a family history of early, devastating complications (low treatment control), or consider the person who reports overwhelmingly distressing emotions following diagnosis. Understanding these common-sense beliefs will guide the educator to potential solutions. A variant of the Health Belief Model, which is a useful screen for potential lack of medication taking, is needs and concerns analysis [74]. Consider a recommendation by a professional to start medication or insulin. Asking the person with diabetes the extent to which they need the medication and the extent to which they have concerns about medication can be accomplished quickly and frames potential adherence challenges. High perceived need and low perceived concern would favour acceptance; high perceived need and high perceived concern suggest ambivalence; low perceived need and low perceived concern suggest indifference; while low perceived need and high perceived concern suggest scepticism. The Health Belief Model can be useful in supporting the acceptance of the diagnosis of diabetes. Supportive counselling can be helpful in empowering the person to come to view diabetes as serious but manageable, in which needs and concerns are addressed and balanced.

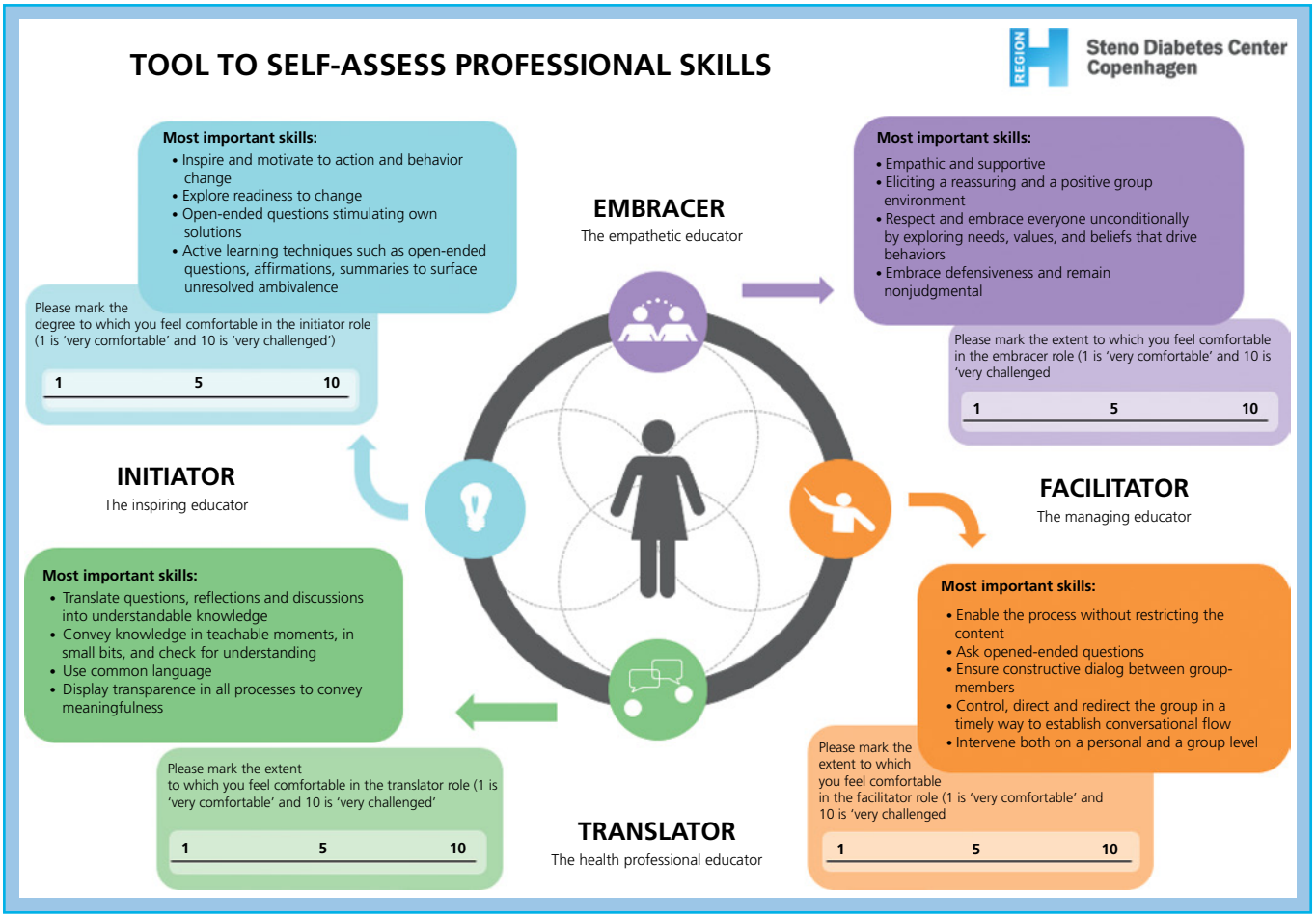

Figure 26.4 Self-assessment tool to develop skills of a person-centred approach in diabetes education and support. Source: Stenov et al. 2017 [71].

Additional theoretical models explaining the drivers of health behaviour have shown great promise in supporting acceptance of disease, acceptance of treatment, and health behaviour change. Prominent among them are social cognitive theory [75], the theory of planned behaviour [76], self-determination theory [77], and the trans-theoretical model [78]. These perspectives help to explain what determines a person's behaviour and can help the educator identify important motivational constructs that are associated with change (Table 26.1).

Perhaps most important are the principles that guide the educator on how to counsel a person with diabetes to help them develop the motivation to change. Here the principles of patient-centredness [79], empowerment [80], and motivational interviewing [81] provide specific knowledge and pathways to guide people towards change. Table 26.2 illustrates the tasks required of people with diabetes and healthcare professionals, and links these guiding principles with theory and constructs that can be brought into the clinical exchange.

Supporting the behaviour change process

Guiding the person towards sustained behaviour change can be understood as using the relationship between the person with diabetes and the healthcare professional to establish four tasks through dialogue and participation [84, 85]:

- *Establishing a change-based relationship*. This is an explicit shift away from the expert teach-and-tell role to one of collaboration and empowerment. It is achieved by recognizing the dangers of a teach-and-tell approach and, using motivational communication, establishes empathy, non-judgmental curiosity, as well as an appreciation of the role of ambivalence. The relationship between the person with diabetes and the healthcare professional achieves common ground regarding the bond alliance, the task alliance, and the goal alliance.
- *Identification of a specific behaviour to change and determining the readiness of the person with diabetes to change that behaviour*. Not being ready to do the work of change is common and readiness is state based, not trait based. This allows one to avoid becoming preoccupied with changing a behaviour that the person is not ready to work on by finding a behaviour that the person is ready to change. Working with those who are ambivalent about change or not ready to change is a fertile area for behaviour change counselling, and virtually the entire content of this chapter speaks to how professionals can support change.
- *Using behaviour modification interventions to promote successful behaviour change*. Numerous behaviour change tools can be implemented when a person is ready to do the work of change.
- *Addressing the psychosocial determinants of behaviour*. Those relational, environmental, and structural issues that make change hard can be addressed. Importantly, with regard to scope of practice, addressing these issues can be successful if the healthcare

Table 26.1 Behaviour change theories in diabetes education.

Theory	Description	Key elements	Application to diabetes education
Social cognitive theory	Specifies determinants of health behaviour, mechanisms through which they work, and ways to translate this knowledge into health practices	Knowledge, perceived self-efficacy, outcome expectations, perceived facilitators, social and structural impediments	Diabetes education should address the determinants of people's health behaviour. The educator can acquire different roles in the education to facilitate this
Self-determination theory	Motivation is either intrinsic or extrinsic and is driven by the needs for competence, autonomy, and relatedness	Assess intrinsic versus extrinsic motivations (doing it for self or for the healthcare team), as well as the impact of self-management on autonomy and connection to others	Diabetes education should promote intrinsic motivation by supporting a person's competence in a way that does not impair connectedness to important others
Theory of planned behaviour	Proposes that the intention to engage in a specific behaviour depends on attitude towards the behaviour, subjective norms regarding the behaviour, and perceived behavioural control	Attitude, subjective norms, perceived behavioural control, intention	Diabetes education should explore attitudes, norms, and perceived behavioural control among individuals to assess their intention to change behaviour
Trans-theoretical model of change/stages of change model	Outlines behaviour change through five stages from a situation where individuals are not aware of a risk to a situation where they are changing their behaviour and fighting relapse	Pre-contemplation, contemplation, preparation, action, maintenance	Diabetes education should guide and support people with diabetes in the process of behaviour change. This includes exploring patient perceptions about importance, confidence, and readiness with regard to behaviour change

Table 26.2 Counselling principles to facilitate self-management motivation.

	Guiding principle	Theoretical model	Example constructs
Person with diabetes			
Faces the personal responsibility to make behavioural choices outside of the clinical context	Health beliefs	Self-regulation model [82]	Perceived consequences, personal control, treatment control, timeline, and emotional impact
	Motivation	Social cognitive theory [75] Theory of planned behaviour [76] Trans-theoretical model [78]	Self-efficacy, perceived social norms, readiness to change/intentions
	Emotion	Diabetes distress scale [83]	Emotional burden, regimen-related distress, physician-related distress, interpersonal distress
Person with diabetes–educator relationship			
The person with diabetes–educator relationship can provide a context to consider new behavioural options and enhance motivation to overcome barriers encountered outside of the clinical visit	Patient-centredness	Patient-centred clinical method [79]	Understand the whole person, explore the person's illness experience, find common ground, and cultivate the relationship to overcome barriers
	Motivational communication	Motivational interviewing [69]	Non-judgmental curiosity, effective use of questioning and listening, working with ambivalence, and supporting self-efficacy
	Empowerment	Person empowerment [43]	Appreciating the process of respecting the autonomy of the person with diabetes

professional adopts the principles of identify, educate, recommend, and support. When a psychosocial issue of relevance is encountered (identify), there is great value in having a healthcare professional assist the person in understanding how the issue affects self-management (educate), increase awareness of how to manage the issue (recommend), and then support the person with diabetes in their efforts to actualize these recommendations.

Recently, a great deal of work has been devoted to integrating the vast array of theories of behaviour change into an overarching model. West et al. examined behaviour change theories, which

included 128 theoretical constructs related to behaviour change, and integrated them into a single framework, called the Theoretical Domains Framework (TDF) [86]. This framework can guide both the development of behaviour change interventions and their implementation. The TDF is made more elegant by its integration into a simplified behaviour change model called COM-B. In this model *Behaviour* is seen to be the result of *Capability, Opportunity*, and *Motivation*. The 128 theoretical constructs related to behaviour change interventions were reduced to 14 domains, which were then integrated in the COM-B perspective [86].

This model has great potential in diabetes education and support. For instance, the healthcare professional and the person with diabetes collaboratively identify a *behaviour* they would like to change. The professional can then assess the factors that might be associated with success in changing this behaviour using this framework. The result of this assessment can identify resources (strengths that the person with diabetes presents that support change) as well as areas for intervention.

Capability involves both psychological and physical components. Physical capability is the skill in the behaviour, where psychological capability involves knowledge, psychological skill, memory, attention, and decision processes as well as behavioural regulation skills. *Opportunity* includes social influence factors as well as environmental context and resources. This comprehensive model has been helpful both from the perspective of designing an intervention as well as guiding the behaviour change counselling within any given interventions. Finally, *motivation* can involve reflective as well as automatic aspects. Reflective motivation results from intentions, goals, beliefs about capabilities, beliefs about consequences, social role and identity, and optimism (six domains). Automatic motivation results from reinforcement, emotion, optimism, and social role and identity (two new domains, two domains overlapping with reflective motivation). Professional counselling to enhance motivation can utilize these constructs as interventions.

Empowerment through language and the flourishing mindset

Several medical journals, national health services, diabetes organizations, as well as academics and professional groups have, during the last decade, advocated for an improvement in the language used in diabetes. As an example, Diabetes Australia and researchers in diabetes psychology provide the following recommendations [87]: 'On average, people with diabetes experience greater emotional distress than those without diabetes. One source of distress can be the language used to refer to diabetes, its management and the person with diabetes. The way verbal and written language is used reflects and shapes people's thoughts, beliefs and behaviours. Language has the power to persuade, change or reinforce beliefs and stereotypes – for better or worse. Words do more than reflect people's reality: they create reality and affect how people view the world and their diabetes.'

An example from the *New England Journal of Medicine* shows how language can be used to anchor the importance of the patient first. Michael Berry and Susan Edgeman-Levitan suggest a substitution of 'What is the matter with you?' with 'What matters to you?' [88]. This shows a movement away from psychopathology *(what is the matter with you?)* to quality of life *(what matters to you?)*.

A useful way of framing the juggling of self-management support roles in DSMES has origins within positive psychology and is described by the American psychologist Martin Seligman as the concepts of learned helplessness and flourishing [89]. Riva Greenberg, an American diabetes activist, has been the leading front person of developing a mindset called the *flourishing mindset*. This mindset builds on positive experiences by focusing on health rather than illness [90]. The operationalization happens by supporting people in finding their innate resilience, particularly through open dialogues aiming to identify what people do well in everyday life and then how to build on that, as opposed to focusing on illness and corrections of behaviour. This can create a relationship of trust, connection, and support between healthcare professionals and people with diabetes, which is the bedrock from which, engaged and encouraged, people can move forward (Table 26.3 and Box 26.1).

Table 26.3 Comparison of coping and flourishing treatment strategies.

Treatment characteristics	Coping mindset	Flourishing mindset
Approach	Cope and repair	Design and build on what is already working
Goal	Come up to 'normal'	Go beyond 'normal' and flourish physically and psychologically
Direction	Avoid what you don't want	Move towards what you do want
Focus	The disease, what is going wrong, and corrective actions	The patient in a personal life context, what is going well, and building on successes
Healthcare provider–patient relationship	The healthcare provider is the expert and decides, tells, and explains what the patient should do	The healthcare provider and the patient are both experts who leverage each other's strengths to co-design a way forward
View of diabetes and impact on one's life	A burden that one must fight/battle/overcome and that makes life smaller/limiting	Bestows benefits, integrates into one's life, and makes life bigger/offers possibilities

Source: Modified from Greenberg and Bertsch 2013 [90].

Outcomes must mirror biomedical as well as behavioural and emotional challenges

One of the most challenging aspects of diabetes education is that diabetes is both a biomedical disease and a behavioural, social and emotional challenge [48, 90, 91]. For positive diabetes outcomes to be realized, the person with diabetes must engage in intentional, effortful, and sustained behaviours. However, the importance of outcomes to the educator (e.g. HbA_{1c} <7.0%, 53 mmol/mol) cannot supersede the importance of outcomes for the person with diabetes (e.g. living life as normally as possible) and things go well only when the two are in synchrony. Thus, the essential outcomes should include biomedical as well as psychosocial outcomes [92].

There is an association between psychosocial problems and poor diabetes outcomes such as risk of hypoglycaemia and frequent omission of prescribed medicine [93, 94]. At the same time, poor diabetes outcomes can cause psychosocial problems, such as

Box 26.1 Tips for working from a flourishing mindset

- Begin each session by asking 'What's improved since we last met?' This encourages the patient to reflect on successes, thereby guiding the visit in a positive direction.
- Ask the patient to share a challenge or difficult life event and describe the steps they took to overcome it. Listen for strengths that were used, provide congratulations, and ask, 'How can you use these strengths to help improve your diabetes management?'
- When looking at a patient's logbook or discussing proposed nutrition interventions, focus on what they are doing well, such as blood glucose numbers that are in range or the two vegetables a week they do eat. Ask 'How did you do this?' and 'What can you do to make this happen more often?'
- Provide patients with suggested areas where improvement is needed and ask them to identify areas of focus and goal setting. Patients are more likely to be successful when they feel ownership for the goal. Discuss ideas for improvement and encourage the patient to implement one or two of them. Even if the selected approach(es) is(are) not successful initially, the patient is more likely to engage in alternative approaches and future recommendations by the healthcare provider if given the opportunity to choose.
- Be present, attentive, and mindful in your visit with a patient. Show genuine curiosity and interest. As is often quoted in medicine, 'Patients don't care how much you know until they know how much you care.'

Source: Modified from Greenberg and Bertsch 2013 [90].

fear of hypoglycaemia, diabetes distress, and functional or occupational interference. Depressive phenomena are common in those with diabetes, particularly diabetes distress. Diabetes distress is distinct from and more prevalent than depression among adults with diabetes [95, 96]. Further, compared to depression, diabetes distress is independently and more strongly associated with suboptimal diabetes self-management and hyperglycaemia [96]. People with diabetes distress may be incorrectly diagnosed as having depression and thus experience an ineffective approach to treatment [97]. A recently published paper by Fisher et al. emphasizes that emotional distress is best considered as a *continuous psychological characteristic*, rather than a distinct *comorbid clinical condition* [98]. In this way, diabetes distress is distinct from mental health disorders and thus is a characteristic to be considered in diabetes education.

While it can be stressful for diabetes educators without a background in psychology to address psychosocial issues within their scope of practice, it can be helpful to know that the ability to communicate one's distress (i.e. to be heard) is often experienced as beneficial in and of itself. If the educator takes the position that they are not the expert and that it is not their responsibility to *fix* the potential problems, then supportive communication can be easier. For instance, it would not be inappropriate for a professional to declare, 'I'd be interested in hearing about what you are going through and possibly make any recommendations that I think might be helpful.' Research indicates a positive association between the presence of physician empathy and better diabetes outcomes [99].

It is also useful for the diabetes educator to be mindful of how diabetes fits into the social world of an individual. The idea of diabetes-specific as well as general social support is important here [100, 101]. People with diabetes can benefit from having sensitive discussions with their diabetes educator about the presence or absence of support from others regarding diabetes self-management. The potential of engaging peers in supporting diabetes outcomes should also be noted [102].

Diabetes self-management education and support in the social context

The second Diabetes, Attitudes, Wishes and Needs (DAWN2) study included a survey of 2057 adult family members of adults with diabetes. According to this study, supporting a relative with diabetes was perceived as a considerable burden by 35% of family members. The study also revealed that 40% of family members experienced high levels of distress related to concerns about their relative with diabetes, and 61% stated they were very worried about hypoglycaemia in their family member with diabetes [103, 104].

People with diabetes generally engage in self-management of their diabetes within a family setting and family members play a role in many everyday tasks such as meal preparation, often providing moral, emotional, and practical support. Thus, struggles with self-management and blood glucose levels, poor well-being, and psychological distress are relevant not only to the individual adult with diabetes. To the contrary, these problems affect – and are affected by – the entire family. Unfortunately, most education programmes exclusively target individuals with diabetes [105–108]. Furthermore, research targeting the interface between adults with chronic disease and their families is relatively scarce and family factors have until recently been virtually ignored in relation to adults with diabetes. A recent study shows how professional support may contribute to the creation of a shared illness identity and a reduction of diabetes-related conflicts within the family as well as enhanced support of self-management [109]. Another study shows that maintaining resilient, good-quality intimate relationships optimizes physical and psychological outcomes for people with diabetes [110]. The vast majority of psychoeducational interventions in type 1 diabetes focus exclusively on people with diabetes, with only a few offering support for family members [95]. However, the importance of partner support is increasingly recognized and its enhancement has become one of the main goals of current psychoeducational interventions in diabetes [111, 112]. The family provides the frame for the potential effects of culture, race, and ethnicity on disease outcomes, and we need to improve our understanding of family influences on diabetes management and ways to engage family members through family-tailored education and support [113].

Appreciation of culture is also essential when considering the context of the person with diabetes. Cultural factors such as self-efficacy, levels of health literacy, and effects of stigma impair accessibility and acceptability to diabetes education [114]. Ethnic minority groups are specifically vulnerable [115, 116]. To reduce the *literacy burden* of ethnic minorities and enhance support for self-management, the cultural context needs to be included to make diabetes education more accessible for all people with diabetes [117, 118].

The final step: using health education tools to promote and support change and self-management

Using cultural probes and design thinking [119] is a promising method in diabetes education. Design thinking is a research method deriving from the design world [120] as well as ethnographic studies [121, 122]. Methods include, for example, the use of postcards with questions concerning participants' attitudes to their lives, maps where participants can highlight areas of importance to their lives, and cameras with instructions asking participants to take photos of important objects. Visual methods similar to cultural probes such as photos, videos, and drawings are often used for data collection [123, 124]. The use of cultural probes in diabetes education is a promising method of translating the theoretical concepts of person-centredness and active involvement into practice to support both educators and people with diabetes. One of the early examples of the use of probes was the Conversation Maps tool, which successfully facilitates interactive dialogue among people with diabetes through relationship building, trust, and confidence as well as the sharing of personal stories and experiences [125]. Further examples are the British Diabetes Education and Self Management for Ongoing and Newly Diagnosed (DESMOND) programme [15] and the Danish NExt EDucation (NEED), Empowerment, Motivation and Medical Adherence (EMMA), and Involvement in families with Type 2 diabetes (PIFT) programmes [126, 127] (Box 26.2).

Box 26.2 Examples of dialogue tools to be implemented to facilitate diabetes self-management education and support

The family mirror

The Family Mirror tool (Figure 26.5) aims to allow each member of a family with diabetes to visualize how they experience the effect of diabetes on their everyday life [128]. Each family member makes a figure of themselves and/or another family member, with the goal of being able to look at diabetes and family life from different perspectives. Further, the aspect of sharing the lived experiences of having diabetes in the family allows for all voices of the family to be heard, as well as the creation of transparency and dialogue on the challenging aspects of living with diabetes in the family's everyday life.

Steps in using the Family Mirror:

- The purpose of the Family Mirror is described.
- Each participant collects a stack of cards and a figure representing themselves and sits across from their relatives.
- The participants make a figure of themselves.
- The participants make a new figure of their relative with the help of the cards.
- The figures are presented within the family. The participants explain which cards they have chosen and why.
- The families share reflections and experience.

Balance cards

Balance cards [126, 129] comprise 27 cards with pictures and quotes (Figure 26.6). The aim of the exercise is to assist participants in talking about the imbalances, challenges, and possibilities they experience in their daily lives with diabetes. The exercise can make it easier for participants to express difficult topics and facilitates dialogue among participants about everyday life with diabetes.

My day

The My Day tool [130] aims to establish a good relationship between the person with diabetes and the educator (Figure 26.7). The educator gains insight into the everyday life of the person with diabetes guided by their focus and needs. This includes valuable information about physical activity, medication taking, social relations, etc.

The person with diabetes is encouraged to discuss their everyday life and challenges, particularly when completing the statement 'It is difficult for me to live with diabetes when…'. A shared understanding is achieved between the educator and the person with diabetes about the challenges involved in living with a chronic illness for specifically this person. This insight allows the educator to acknowledge the difficulties the person with diabetes is going through by including these dynamics in their relationship.

Evaluation of diabetes education

Given the potential positive role that DSMES can have on people living with diabetes and their family, perhaps the most important indicator in the evaluation of diabetes education is the availability of and access to diabetes education. Biological outcome measures have for a long time dominated the evaluation of diabetes education, which is unsurprising as they make up essential outcomes in diabetes. In reviews and meta-analyses of diabetes education, the most used outcome measures can be divided into four categories: biological, behavioural, knowledge, and psychosocial outcomes. Most attention has been paid to biological outcomes, particularly HbA_{1c}, and knowledge-based outcomes. Less attention has been placed on behavioural outcomes and least on psychosocial outcomes [131].

An interesting and useful perspective, which is consistent with the complexity of diabetes education, is to examine the mechanisms by which an education programme works [132, 133]. If an education programme is found to be effective, how do we know what to replicate and what to change when we implement the programme somewhere else? Why do some programmes work in one place for one group of participants and not for another? Focusing on mechanisms of effects is complicated, as the education process typically involves multiple interacting components. It is thus difficult to identify the precise mechanisms leading to effects of the various components [134, 135]. Further, outcomes depend on the competencies of educators and the preconditions and motivation of participants as well as organizational conditions, all of which may be difficult to capture in a randomized controlled trial [135]. In response to this, theory-driven forms of evaluation have gained attention, as they can generate knowledge about the effectiveness of an education programme as well as knowledge about the underlying mechanisms of effects [136, 137].

Theory-driven evaluation comprises 'an explicit theory or model of how the program causes the intended or observed outcomes and an evaluation that is at least partly guided by this model' [137]. Thus, a core element of theory-driven forms of evaluation is the development and use of theory in the evaluation process. The theory, often referred to as programme theory, specifies relationships between intervention actions and intended outcomes [136].

An education programme is an incarnated theory of change: a theory about how to change problematic conditions or behaviour.

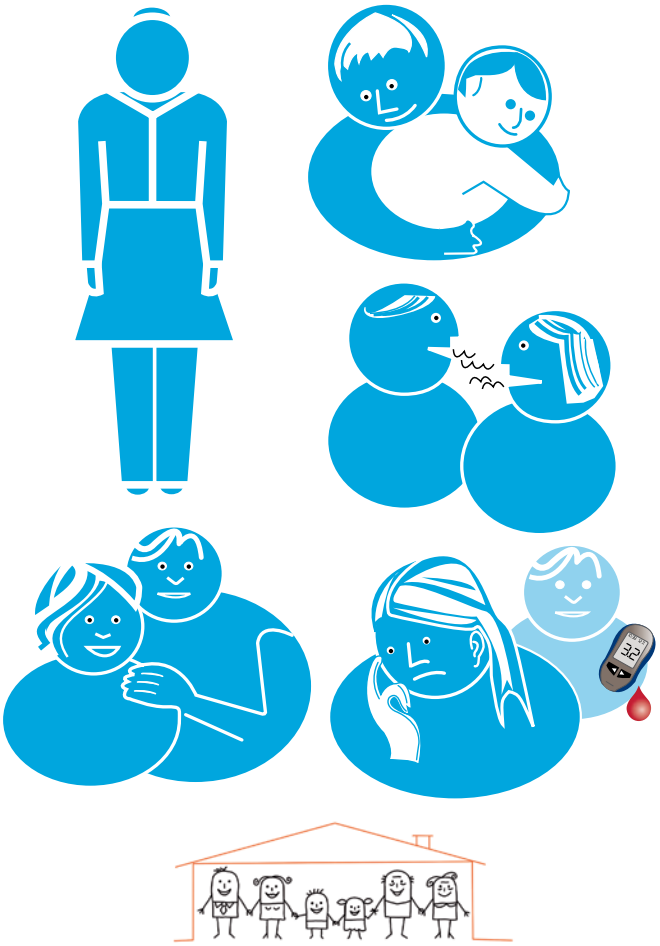

Figure 26.5 The family mirror.

Figure 26.6 Balance cards.

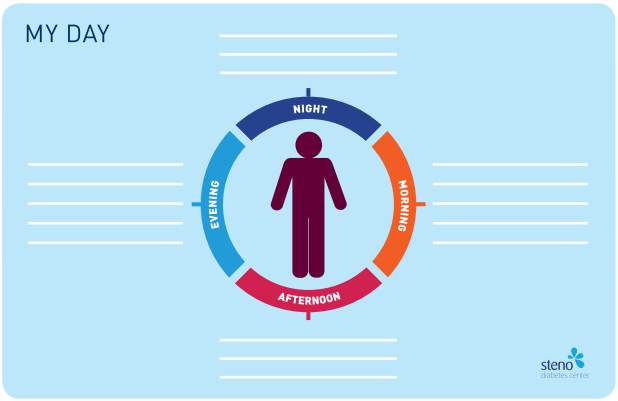

Figure 26.7 My day.

However, this theory is often unrecognized or poorly articulated, perhaps since a programme is an active open system that:

- Is apt to change over time as the programme unfolds.
- Works through the ideas and intentions of those implicated.
- Works differently among different subgroups.

Pawson and Tilley [138] describe the realistic evaluation approach, which focuses on three key concepts for understanding how, for whom, and under what conditions programmes will work: *most effective outcomes*, *mechanisms* through which outcomes occur, and *contexts* where the outcomes potentially will be replicable. Mechanisms refer to the process of how people interpret and act on the intervention to produce outcomes. Mechanisms are not assumed to be fixed, but are contingent on contexts. Thus, the programme theory can be expressed as context–mechanism–outcome configurations (C–M–O configurations). The evaluation implies the development of a theory about how outcomes, mechanisms, and contexts operate and use of this theory to direct empirical work. The evaluation focuses on exploring whether the theory can explain the observational data [138]. In a recent review regarding use of realistic evaluation, the use of C–M–O configurations was found to provide clarity in complex evaluation environments and rich information about what type of interventions work for whom in what context [139].

Table 26.4 shows a programme theory. If a person with diabetes is recruited to the programme and completes it, and if the programme takes a specific educational approach, then the person will attain improved knowledge and skills related to the management of diabetes and increased autonomy and quality of life. Working with programme theory, ideally a second level of data collection and analysis is needed in order to evaluate whether (i) the theory is right but not properly implemented; (ii) the theory should be refined; or (iii) the theory is wrong. Table 26.5 gives the key points in programme theory.

Conclusion

The provision of DSMES based on evidence, values and theories, skills, and tools (Figure 26.1) [35] is a challenging task; however, the evidence base of the beneficial effects of this approach is rapidly increasing. Self-management education is considered a complex intervention [140] with many different components, actors, and settings, leading to challenges in identifying the most effective components. Therefore, it is difficult to assess the effect of a single tool or method, or whether specific combinations of tools and methods or

Table 26.4 Programme theory.

Context	Mechanisms	Outcomes
The specific diabetes education programme or concept is applied: • Involvement, dialogue • Integrates cognitive, emotional, and bodily elements • Facilitates exchange of experience	The participants reflect on their experiences and feelings and share them with other participants and the educator	The participants increase their knowledge and confidence in relation to diabetes self-management
The educator has the skills to juggle, facilitate, and motivate, and is empathic	Educator talk ratio <40% on average	The participants increase their well-being
	The participants feel involved in the education process and experience that their individual needs are met	The participants engage in health-promoting behaviour
		The participants improve as regards articulated outcomes of the programme

Table 26.5 Key points in programme theory.

- Realistic evaluation is about theory testing and refinement
- Realistic evaluation develops and tests context–mechanism–outcome (C–M–O) configurations (hypotheses) empirically
- Realistic evaluation applies any approaches, tools, and methods that are appropriate to test a programme theory
- Realistic evaluation is potentially time-consuming as there is no independent criteria for closure

the quality or quantity makes interventions effective [141]. However, the Health Foundation in the UK identified effective elements of the implementation of 11 programmes of self-management support and shared decision making in chronic disease, including diabetes [141].

Figure 26.8 summarizes the points made in this chapter. A limiting factor of diabetes education is that it almost always does not include ongoing education and support. Once people with diabetes complete an education programme in its entirety, they are not provided with a component of ongoing support to allow tailoring of the education to their continued diabetes care needs. The 'once' education becomes education for life and therefore conclusive, without any opportunity for an information refresher or support mechanism that may be needed to adjust to changes in the perceived needs and preferences of people with diabetes. The lifelong process of diabetes self-management requires continued adjustments in knowledge, skills, motivation, and support. DSMES should be a lifelong process, starting at the point of diagnosis and remaining as an essential component of diabetes care [142].

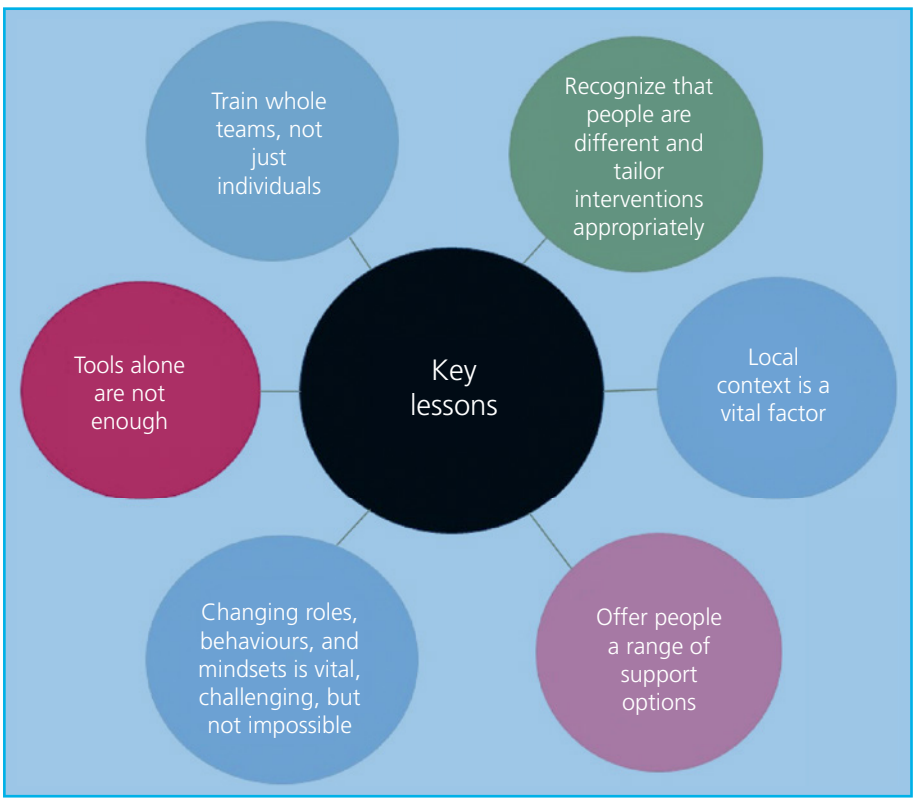

Figure 26.8 Principles for effective diabetes education and support. Source: Based on Ahmad et al. 2014 [141].

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27 Dietary Management of Diabetes

Nicola Guess
Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

Key points

- Weight loss is a primary mediator of diabetes risk reduction and management of type 2 diabetes in those who have overweight or obesity.
- Calorie content and maintenance of the diet are more important than macronutrient content for successful weight loss maintenance.
- The type and quality of dietary fat and carbohydrate are more important than amounts of these macronutrients for prevention and management of diabetes and its complications.
- Various dietary patterns are effective for weight loss, and for diabetes and cardiovascular risk reduction, and clinicians should consider individual preferences.
- Matching carbohydrate to insulin dose, either as part of multiple daily insulin or continuous subcutaneous insulin regimen, is the most effective approach for the management of glycaemia in type 1 diabetes.
- Women with diabetes planning to become pregnant should take 5 mg of folic acid per day to prevent neural tube defects.
- Calorie restriction to lose weight should not currently be recommended during pregnancy, but limiting weight gain can improve pregnancy outcomes.
- Low–glycaemic index foods may help manage blood glucose concentrations during pregnancy.

Diet plays an important role in the effective management of type 1 diabetes and type 2 diabetes and is fundamental to the prevention of type 2 diabetes. The aim of nutritional management of diabetes is to optimize glycaemic and blood pressure management, correct any lipid abnormalities, and, in doing so, reduce the risk of long-term complications [1–3]. Dietary advice must be evidence based and individualized, taking into account personal and cultural preferences, and ensuring the diet is appropriate and compatible with the person's lifestyle, existing treatment regimen, other comorbidities, and willingness to change [1–3].

Individuals with diabetes are up to four times more likely to develop cardiovascular disease [4, 5], with an elevated risk also seen in impaired glucose tolerance [5] compared to individuals with normoglycaemia. Therefore, evidence-based nutritional recommendations for individuals with diabetes are based on the glucose management of the diabetes, reducing the risk of developing cardiovascular disease and the complications of diabetes [1–3]. The strength of evidence for the different nutritional recommendations for both management of diabetes and prevention of cardiovascular disease is graded according to the type and quality of published studies as well as statements from expert committees [2]. The gold standard for evidence-based guidelines is meta-analyses of large, well-controlled trials with long follow-up periods that include fatal or non-fatal clinical endpoints. However, this information is often not available and instead surrogate endpoints, such as glycaemia, body composition, lipoprotein profile, blood pressure, insulin sensitivity, and renal function, are used to determine the potential of dietary modification to influence glycaemic levels and risk of acute and chronic complications of diabetes [1, 2].

There are many confounding factors within long-term dietary trials in diabetes, which limit the precision of such trials to establish effectiveness. These include but are not limited to differences in weight loss [2], medication withdrawal [6], and the composition and intensity of the control diet [7]. Adherence to a dietary trial protocol tends to lapse over time, which often means that intended differences in the dietary composition of intervention and control arms diminish in long-term trials [8]. While short-term trials can often achieve better adherence to a dietary intervention [9], the external validity of these trials to understand the long-term effect of diet on chronic disease management is poor. Each of these factors should be considered when interpreting findings from meta-analyses of nutritional interventions.

While nutritional science illuminates the underlying mechanisms of diet on disease risk, in practice nutrients are consumed as foods and as part of dietary patterns. Therefore, throughout this chapter, while reference will be made to the impact of individual macro- and micronutrients on clinical outcomes, it is important to consider how these nutrients form part of an overall healthful dietary pattern for diabetes prevention and management. Tables 27.1 and 27.2 summarize such dietary approaches.

Energy balance and body weight

Weight management is now understood to be the primary strategy for prevention of type 2 diabetes and for glycaemic management in people with type 2 diabetes who have overweight or obesity [1, 2]. Weight gain is associated with an increased incidence of type 2 diabetes [10],

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Table 27.1 The association of particular dietary components with risk or management of type 2 diabetes, and their inclusion or exclusion in established dietary patterns or guidelines.

Dietary components	Mediterranean	DASH	Diabetes UK	NICE	Effect on diabetes management/risk
Fruit	×	×	×	×	Dietary fibre associated with reduction of risk
Vegetables	×	×	×	×	Dietary fibre associated with reduction of risk
Nuts/seeds	×	×	×	×	↑ PUFA/MUFA to SFA ratio associated with reduction in FPG, HbA_{1c}, and insulin resistance Insoluble fibres associated with reduction in risk of diabetes Magnesium associated with reduction in risk of diabetes
Pulses	×	×	×	×	Soluble fibres reduce post-prandial glucose in randomized controlled trials. Low GI is associated with reduction of risk, and reduces HbA_{1c} by 5 mmol/mol (0.5%)
Fish and seafood	×		×	×	No known effects of omega-3 on diabetes management or risk
Increased white to red meat ratio			×	×	↑ PUFA/MUFA to SFA ratio associated with reduction in FPG, HbA_{1c}, and insulin resistance
Wholegrains/ cereal fibre	×	×	×	×	Insoluble fibres associated with reduction in risk of diabetes Magnesium associated with reduction of risk of diabetes
Low glycaemic index			×	×	Associated with reduction of risk, and reduces HbA_{1c} by 5 mmol/mol (0.5%)
Olive oil	×				↑ PUFA/MUFA to SFA ratio associated with reduction in FPG, HbA_{1c}, and insulin resistance
Vegetable oil (sunflower, rapeseed oil)			To replace butter and SFA spreads	To replace butter and SFA spreads	↑ PUFA/MUFA to SFA ratio associated with reduction in FPG, HbA_{1c}, and insulin resistance
Low-fat dairy		×	×	×	Dairy intake associated with reduction of risk; milk proteins may lead to reduced glucose concentrations and increased insulin secretion. Vitamin D and calcium associated with reduction of risk
Alcohol	Moderate	↑			Moderate intake associated with reduction of risk
Decreased red or processed meat					Diets high in red, especially processed, meat associated with increased risk of diabetes
Butter	Limited		Replaced with non-SFA spreads	Replaced with non-SFA spreads	↓ PUFA/MUFA to SFA ratio associated with increased risk of diabetes, FPG, HbA_{1c}, and insulin resistance
Sweetened beverages		×	Limit	Limit	Sugar-sweetened beverages associated with increased BMI, leading to increased risk of diabetes
Sodium					No known effects of omega-3 on diabetes management or risk

× = included in dietary pattern.
These data are largely derived from observational studies. Orange indicates components with a protective association; blue indicates components with a deleterious association.
BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension; FPG, fasting plasma glucose; GI, glycaemic index; HbA_{1c}, glycated haemoglobin; MUFA, monounsaturated fat; NICE, National Institute for Health and Care Excellence; PUFA, polyunsaturated fat; SFA, saturated fat.

while weight loss reduces insulin resistance and improves glucose handling in people with and without diabetes [11]. A series of large-scale, lifestyle-based randomized controlled trials [12,13] have conclusively shown that a 5–7% weight loss in people at risk of diabetes reduces risk by up to 66% (Figure 27.1). While these programmes also included other components such as increasing fibre, decreasing total and saturated fat, and increasing physical activity, weight loss was the primary driver of the reduction in risk [14]. A trial testing the independent effect of dietary fibre on type 2 diabetes development did not find that it significantly reduced the risk of type 2 diabetes [15]. Interestingly, there also appears to be a legacy effect of weight loss on diabetes prevention, such that even three years after the intervention stopped, there was still a 48% risk reduction in the intervention group [16].

Each of the large-scale type 2 diabetes prevention trials tested a similar dietary pattern: low fat, with some of the trials specifying low saturated fat and/or high fibre. One recent multinational trial compared a high- versus low-protein diet and did not find that the protein content influenced the risk of type 2 diabetes [17]. However, prior to randomization to the high- or low-protein groups, all participants had undergone an intensive weight loss intervention and

Table 27.2 The association of particular dietary components with risk of cardiovascular disease, and their inclusion or exclusion in established dietary patterns or guidelines.

Dietary components	Mediterranean	DASH	Diabetes UK	NICE	Effect on cardiovascular disease risk
Fruit	×	×	×	×	Dietary fibre associated with reduction of risk
Vegetables	×	×	×	×	Dietary fibre associated with reduction of risk
Nuts/seeds	×	×	×	×	↑ PUFA/MUFA to SFA ratio associated with reduction in LDL, neutral effect or ↑ HDL, reduction in cardiovascular disease risk Dietary fibre associated with reduction in risk of cardiovascular disease
Pulses	×	×	×	×	Dietary fibre associated with reduction in risk of cardiovascular disease Low glycaemic index associated with reduction in risk
Fish and seafood	×		×	×	No known effects of omega-3 on diabetes management or risk
Increased white to red meat ratio			×	×	↑ PUFA/MUFA to SFA ratio associated with reduction in LDL, neutral effect or ↑ HDL, reduction in cardiovascular disease risk
Wholegrains/cereal fibre	×	×	×	×	Dietary fibre associated with reduction in risk of cardiovascular disease
Low glycaemic index			×	×	Associated with reduction of risk
Olive oil	×				↑ PUFA/MUFA to SFA ratio associated with reduction in LDL, neutral effect or ↑ HDL, reduction in cardiovascular disease risk
Vegetable oil (sunflower, rapeseed oil)			To replace butter and SFA spreads	To replace butter and SFA spreads	↑ PUFA/MUFA to SFA ratio associated with reduction in LDL, neutral effect or ↑ HDL, reduction in cardiovascular disease risk
Low-fat dairy		×	×	×	No consensus on effect of dairy on cardiovascular disease risk
Alcohol	Moderate	↑			Moderate intake associated with reduction of risk
Decreased red or processed meat					Diets high in red, especially processed, meat associated with increased risk of diabetes
Butter	Limited		Replaced with non-SFA spreads	Replaced with non-SFA spreads	↓ PUFA/MUFA to SFA ratio associated with increased LDL concentrations and cardiovascular disease risk
Sweetened beverages		×	Limit	Limit	Sugar-sweetened beverages associated with increased BMI, leading to increased risk of cardiovascular disease
Sodium					Sodium restriction reduces blood pressure and cardiovascular disease risk

× = included in dietary pattern.
Orange indicates components with a protective association; blue indicates components with a deleterious association.
BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MUFA, monounsaturated fat; NICE, National Institute for Health and Care Excellence.

lost about ~10 kg over eight weeks. This type of intervention "reboots" the pancreatic β cells and normalizes blood glucose concentrations in type 2 diabetes [18], and likely would have done the same in people with pre-diabetes. Therefore, at the present time, it is unknown whether the addition (or reduction) of specific nutrients or food groups within a weight loss intervention could optimize type 2 diabetes prevention programmes.

Remission of type 2 diabetes

Remission of type 2 diabetes refers to the normalization of blood glucose concentrations in the absence of anti-diabetes medications, although there is currently no consensus on the exact definition. While numerous short-term studies have shown that marked caloric restriction can normalize the underlying pathophysiology and hyperglycaemia of type 2 diabetes [19], until recently it was not known how enduring this *normalization* could be. The DiRECT trial (Diabetes Remission Clinical Trial) published in 2017 showed that remission of type 2 diabetes can be long-lasting, but is dependent on both the achievement and maintenance of substantial weight loss, in the order of 10–15 kg [18, 20].

Remission appears to be contingent on the return of the first-phase insulin response [21]. The first-phase insulin response declines along the pathway of type 2 diabetes: it is reduced in newly diagnosed type 2 diabetes and nearly absent in type 2 diabetes of long duration [22]. It appears that return of the first-phase insulin

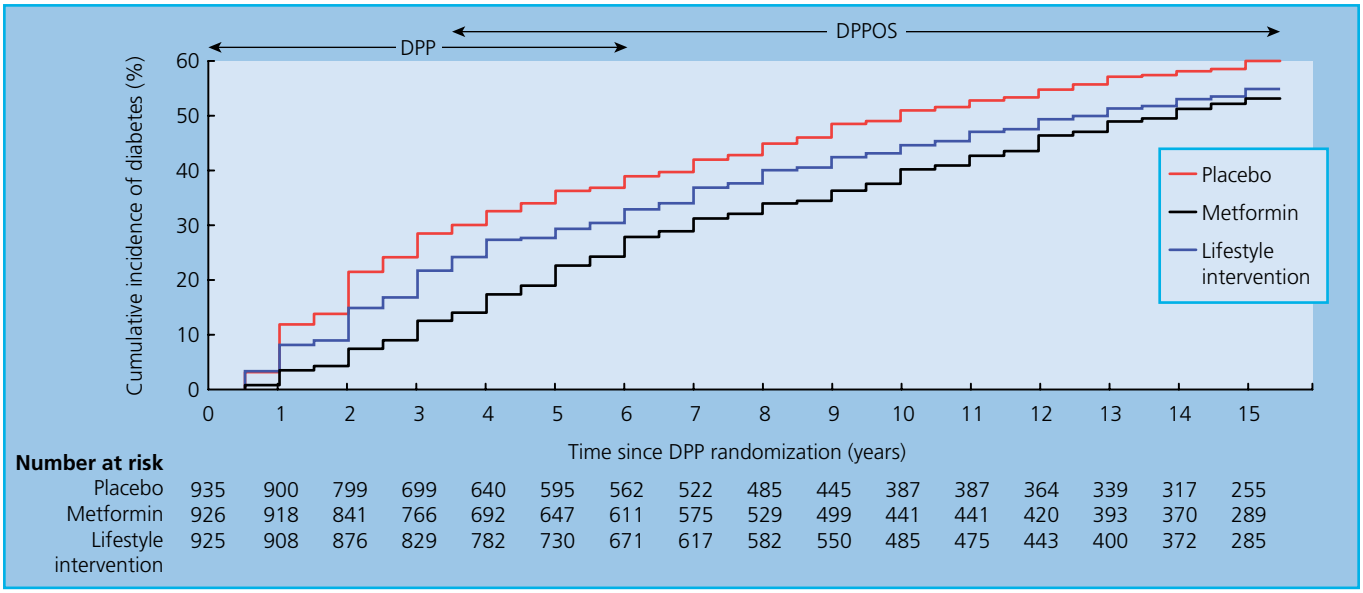

Figure 27.1 Reduction in the incidence of diabetes in the US Diabetes Prevention Program (DPP). This figure shows the data from the DPP itself and data from the follow-on Diabetes Prevention Program Outcomes Study (DPPOS), which followed the same individuals up to 15 years. Source: Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: The Diabetes Prevention Program Outcomes Study. *Lancet Diabetes Endocrinol* 2015; **3**(11):866–875. Copyright 2015 Elsevier.

response can occur in type 2 diabetes of short duration (within approximately 4–6 years of diagnosis), but is much less likely in type 2 diabetes of long duration [21].

As an emerging area of research, there are many unknowns surrounding remission of type 2 diabetes, including whether it can occur with more modest weight loss; and whether other dietary strategies, particularly low carbohydrate, could increase the rate of remission and prevent relapse to type 2 diabetes. Currently available data suggest that ketogenic or high-protein, low-carbohydrate diets could help achieve remission, potentially via mechanisms independent of weight loss [23,24] but longer-term and/or controlled studies are needed to confirm this.

Weight loss also reduces important cardiovascular risk factors, including circulating triglycerides and blood pressure [2]. A systematic review of studies with at least two years' follow-up showed that intentional weight loss in people with type 2 diabetes reduces their mortality risk by 25%, with a higher risk reduction with greater weight loss [25]. The LookAHEAD (Action for Health in Diabetes) study found that an intensive lifestyle for primary prevention of cardiovascular disease did not significantly reduce cardiovascular disease–related morbidity or mortality after nearly 10 years of follow-up [26]. However, this may reflect the limitations of dietary improvements in long-term mortality in people treated aggressively with antihypertensive and lipid medications [27], and does not discount the role of weight loss and dietary change in improving quality of life [27], reducing intensification of medical treatment of diabetes and cardiovascular disease, and greater physical functioning [26,27]. Reductions of 5–10% are effective at reducing cardiovascular risk factors and are achievable and feasible, although greater weight loss may reduce risk further [28].

Weight management has also been considered for people with type 1 diabetes, as the prevalence of overweight and obesity is increasing in type 1 diabetes [29] and the co-presentation of insulin resistance is associated with hyperglycaemia [30]. However, there is little evidence that body weight or weight loss influences glycaemic levels in people with type 1 diabetes [29]. Furthermore, in both type 1 and type 2 diabetes, caution should be applied to intentional versus unintentional weight loss, as unintended weight loss in people with diabetes may also be an indication of suboptimal medical management or omission or inadequate dosing of medications leading to hyperglycaemia [31].

Therefore, national [32–34] and international guidelines [5] recommend initial weight loss of 5–10% in those with overweight or obesity for the purposes of type 2 diabetes management and prevention of type 2 diabetes and cardiovascular disease.

Currently there is no consensus on the optimal diet to achieve and maintain the recommended weight loss [1]; however, the overall energy content of the diet is more important than macronutrient composition [2,35,36]. Effective strategies for which there is evidence in people with diabetes include low-carbohydrate [37], low–glycaemic index (GI) [38], low-fat [28], or very low-calorie diets [39], and meal replacement [40]. There has been particular interest in low-carbohydrate diets, which appear to be most effective at promoting weight loss over the short term, and may also have beneficial effects on glycaemia independent of body weight [41,42] and greater withdrawal of type 2 diabetes medications [42]. While there is little evidence for superiority over the long term [43,44], practitioners should be open to this approach and individual preference. The primary factor in achieving and maintaining weight loss remains long-term maintenance of the diet, and the best approach is therefore one that fits with a person's lifestyle, habits, and goals [1,2].

Carbohydrate and diabetes

The relationship between carbohydrate intake and glycaemia in type 2 diabetes is not straightforward and currently there is no definitive evidence that carbohydrate reduction *per se* durably lowers

glycaemia. However, carbohydrate intake remains the primary determinant of glycaemic levels in people with type 1 diabetes [1].

Quantity

There is no evidence for a specific quantity of carbohydrate in the diet for the management of type 2 diabetes [1]. The trial evidence is severely limited by varying amounts of carbohydrate being prescribed in the low-carbohydrate arm, the actual carbohydrate amount and type being consumed throughout the trial, whether or not anti-diabetes medications were taken or withdrawn during the trial, the protein content of the dietary arm, and differences in weight loss achieved. Physiological studies [41] and short-term trials [24] indicate that the ketones produced on a very low-carbohydrate (ketogenic) diet could help lower blood glucose independent of weight loss, perhaps by reducing hepatic glucose output [45]. Trial evidence [46,47] shows that nutritional ketosis is an effective option for the management of type 2 diabetes, but whether it is superior to other approaches requires better controlled trials.

There are no randomized controlled trials investigating eucaloric carbohydrate restriction and risk of diabetes, but epidemiological data suggest there is no relationship between total carbohydrate intake and risk of type 2 diabetes [48]. Based on the currently available evidence, the quality and source of carbohydrate are more important than total amount for the prevention of type 2 diabetes.

In contrast, carbohydrate counting forms the basis of the management of type 1 diabetes, where recommended carbohydrate intake should take account of energy requirements, blood glucose concentrations, and insulin dosing [49,50]. Carbohydrate counting is a meal planning approach that involves matching 10 g or 15 g carbohydrate portions to a particular bolus insulin dose [49], and is based on the premise that carbohydrate is the primary driver of post-prandial glucose concentrations [51]. As a concept, carbohydrate counting has been around since the 1920s, but has been widely employed since its use in the Diabetes Control and Complications Trial [52]. It is now the dietary strategy of choice in type 1 diabetes. Approaches to carbohydrate counting can vary immensely between country, region, institution, and individual practitioner, but may include the following:

- Carbohydrate awareness.
- Basic carbohydrate counting and label reading.
- Development of the person's skills in monitoring and recording blood glucose levels in relation to food intake, medications, and physical activity.
- Sophisticated matching of carbohydrate to insulin dose. This may include the use of wizard bolus meters or apps to aid in the estimation of carbohydrate intake and insulin requirement.

These techniques should enable the person with type 1 diabetes to add or subtract short- or rapid-acting insulin at meals and snacks to manage and correct blood glucose levels [49,53]. The heterogeneity in these approaches must be taken into account when interpreting the evidence for carbohydrate counting [54].

Adjustment of insulin to carbohydrate intake

In people with type 1 diabetes treated with multiple daily insulin or continuous subcutaneous insulin infusions, carbohydrate counting with insulin dose adjustment is an effective approach to lower glycated haemoglobin (HbA_{1c}), reduce the occurrence of hypoglycaemic episodes, and improve quality of life and other clinical markers such as body mass index (BMI) and waist circumference [3,53,55,56]. However, there is a need for good-quality education, and appropriate clinical support is necessary to ensure accurate and consistent insulin dose adjustments [3,57]. Inaccuracy in carbohydrate counting or dose adjustment is common, and is associated with poorer clinical outcomes [58]. Care must be taken to ensure that carbohydrate counting and dietary advice are not detrimental to an individual's weight management goal. Additional snacks are not automatically required and should be tailored to the individual's needs. Referral to a structured education programme of proven benefit is recommended, such as the DAFNE (Dose Adjustment For Normal Eating) programme, ideally 6–12 months after diagnosis [3]. In individuals with fixed or biphasic insulin regimens, consistency in carbohydrate intake is recommended and is associated with reductions in HbA_{1c} [3,59,60].

A small number of recent studies have suggested that the fat and protein content of the meal should also be taken into account when planning an insulin regimen [61,62]. However, any potential physiological benefits of these approaches need to be balanced with the complexity and burden for the person with diabetes.

Carbohydrate in the treatment of mild to moderate hypoglycaemia

Mild or moderate hypoglycaemia is a common occurrence with insulin treatment in both type 1 diabetes and type 2 diabetes. Glucose is the most effective treatment and should be given immediately [3]. National and international guidelines recommend 15–20 g should be given straight away (Box 27.1), followed by another 15 g if blood glucose does not rise by 4 mmol/l after 15 minutes [49]. A follow-up carbohydrate snack (15–20 g) may be necessary to reduce the risk of further hypoglycaemia, particularly in circumstances where blood glucose is likely to continue to decrease, such as following alcohol consumption or physical activity [49].

Carbohydrate quality

Dietary carbohydrates represent a heterogeneous group of compounds, which include glucose, cellulose, fructose, lactose, starch, resistant starch, sucrose, oligosaccharides, and lignin. The diverse effects of these different structures [63] on diabetes and metabolic risk factors are too numerous to expand on in this chapter, but these factors emphasize the limitations of such terms as a high- or low-carbohydrate diet. Nevertheless, the *quality* of these different carbohydrates can be imperfectly but usefully captured by use of the glycaemic index.

The GI is an indication of the glucose-raising potential of the carbohydrate, and is defined by the incremental area under the blood glucose curve (iAUC) as a percentage of each person's average iAUC for a standard food, usually 50 g glucose or white bread [64]. The glycaemic load, which is the product of the dietary GI and total dietary carbohydrate, may also be used to express the overall quality of carbohydrate in the diet [65].

In people with type 2 diabetes, a Cochrane review of randomized controlled trials suggests adoption of a low-GI diet can lead to

Box 27.1 Foods containing 15–20 g of fast-acting carbohydrate

- Small glass of sugary (non-diet) drink
- At least three glucose tablets
- Five sweets, e.g. jelly babies
- Small carton of pure fruit juice
- Glucose gel

HbA_{1c} reductions of 5 mmol/mol (0.5%) [65]. While data from epidemiological studies suggest low-GI diets are associated with a lower BMI [66], randomized controlled trials have demonstrated a reduction in HbA_{1c} independent of changes in body weight [67,68]. Low-GI diets are associated with a lower risk of type 2 diabetes [69], but there are no controlled trials examining the effect of the GI on type 2 diabetes incidence as a primary outcome.

The evidence of effectiveness of low-GI diets in management of glycaemia of type 1 diabetes is unclear [2] and the latest National Institute for Health and Care Excellence (NICE) guidelines do not recommend their use in people with type 1 diabetes [3].

Low-GI diets may also reduce cardiovascular disease risk by lowering triglyceride and low-density lipoprotein (LDL) cholesterol levels [70]. However, current guidelines do not make specific recommendations regarding GI and cardiovascular disease risk.

Dietary fibre

The indigestible nature of dietary fibres renders them low or non-glycaemic [63,71]. However, dietary fibres themselves and foods high in fibre appear to influence glucose homeostasis beyond their GI [72,73]. Increasing dietary fibre by approximately 18 g/d up to a total intake of 50 g/d leads to a reduction in fasting plasma glucose of 0.7–0.9 mmol/l [72,74] and in HbA_{1c} of 4 mmol/mol (0.3%) [72]. However, according to the American Diabetes Association, there is insufficient evidence to recommend people with diabetes consume fibre in amounts exceeding the current recommended daily allowances (RDA) [75]. Furthermore, the majority of people in Western populations do not meet the minimum recommendations, and targeting this should be a dietary priority.

Dietary fibre is inversely associated with diabetes risk in cohort studies [76]. In the Finnish Diabetes Prevention Study, participants were advised to consume 15 g/1000 kcal of fibre [13], which appeared to reduce diabetes risk, an effect partly independent of its effects on body weight [77]. Current guidelines for diabetes prevention recommend increasing fibre intake to reduce diabetes risk [2].

Epidemiological data support a protective role of dietary fibre against cardiovascular disease, with the data most consistent for wholegrains [78]. There are currently insufficient data from randomized controlled trials, and current guidelines do not make specific recommendations for the role of fibre in cardiovascular disease risk.

Dietary mono- and disaccharides

Sucrose

Despite controversy about the role of sugar in diabetes management, moderate intake of sucrose (10–15% total energy) or other added sugars can be included in the diet of people with diabetes without worsening glycaemic levels or insulin sensitivity [2,60,79–81]; however, care must be taken not to exceed energy requirements [2,60,82]. In a randomized controlled trial, there was no difference in insulin resistance after six weeks of 25% versus 10% of energy from sucrose in healthy people [79]. In contrast, 1 l per day of a sucrose-containing beverage increases hepatic lipid deposition compared to isocaloric quantities of milk, water, or aspartame-sweetened beverages [83]. There is no definitive evidence that sucrose *per se* influences cardiovascular disease risk, but the totality of the evidence supports limiting or avoidance of sucrose as a prudent dietary strategy [84]. In summary, recommendations for sucrose intake for people with or at risk of diabetes are based on those for the general population, namely limiting the consumption of energy-dense, nutrient-depleted sucrose.

Fructose

Fructose is a low-GI monosaccharide and isocaloric exchange of fructose for other carbohydrate improves glycaemic levels in people with type 2 diabetes over the short term, even when consumed up to 160 g/day [85]. However, the metabolism of fructose leads to processes detrimental to human metabolism, including increased *de novo* lipogenesis, higher ectopic lipid accumulation, and elevated triglycerides and uric acid, leading to non-alcoholic fatty liver disease and increased cardiovascular risk [86]. While there is a need to identify the optimal quantity of fructose that improves glycaemia without deleterious cardiometabolic effects [87], a variety of fruits and vegetables are to be encouraged as part of an overall dietary pattern [2] (Tables 27.1 and 27.2).

Non-nutritive sweeteners

The non-nutritive sweeteners approved for use in the UK and Europe include aspartame, saccharin, acesulfame potassium, cyclamate, and sucralose [88]. The increased sweetness of these compounds means they are consumed in miniscule amounts in the diet, and recommendations for people at risk of or with diabetes are the same as the general population [89]. These sweeteners do not contribute to energy intake or influence glucose levels [89]. Other sweeteners commonly used are sugar alcohols. While they are moderately glycaemic, sugar alcohols are consumed in such minor amounts that their consumption does not require alterations in insulin adjustment [2].

Dietary fat

The role of dietary fat in diabetes management has been of interest for decades following observations in the 1950s that dietary fat can modify insulin signalling [90] and the association between saturated fat and cardiovascular disease [2,91]. However, there appears to be little association between total fat in the diet and risk of diabetes [90]. Although diabetes prevention programmes have limited total fat [12,13], weight reduction *per se* and not macronutrient composition of the diet was the primary driver of risk reduction [14]. Similarly, there is no consensus on percent calories from fat in relation to diabetes management [2,90]. Instead, the types and sources of fat consumed and total quality of the diet appear to be more important.

Saturated fat

Replacement of saturated fat (SFA) with polyunsaturated fat (PUFA) is associated with a reduction in diabetes risk in multiple cohort studies [90,92]. The evidence is stronger for replacement with PUFAs than monounsaturated fatty acids (MUFAs), but this may reflect the close association of MUFAs with SFAs in Western diets and the availability of biomarkers for PUFA intake in prospective studies [90]. Data from randomized controlled trials do not consistently demonstrate a detrimental effect of SFA on insulin sensitivity [93–95], but methodological differences in these studies, such as sample size, duration, and the macronutrient that replaces SFA, may explain these inconsistencies.

The proposed relationship between SFA and cardiovascular disease largely arose based on early population studies [96]. However, several updated meta-analyses have questioned the conclusion that simply reducing SFA intake will necessarily reduce cardiovascular disease prevalence [97,98]. Instead, replacing the macronutrient

appears to be important: replacement of SFA with refined but not high-quality carbohydrate or unsaturated fat has been linked to worsening of atherosclerotic risk factors including elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol, and increased concentrations of small, dense LDL particles [97–101], emphasizing the need to consider the quality of the diet as a whole.

Similarly, recent studies have also drawn attention to the heterogenic nature of dietary fat classes, with short-chain, long-chain, and odd-chain SFAs associated with diabetes risk reduction, and medium-chain SFAs associated with increased risk [102, 103]. Odd-chain fatty acids are predominantly found in dairy products, but whether or not these fatty acids have beneficial effects *per se* or whether these associations reflect other nutrient components found in dairy is currently unclear.

Similarly, SFAs come from a variety of food sources, including red and processed meats, dairy products, nuts, and oils, and a prudent approach is therefore to promote foods associated with healthful dietary patterns such as nuts, seeds, oils, low-fat dairy, fish, and fruit and vegetables, and to limit red (particularly processed) meat and butter (Tables 27.1 and 27.2).

In summary, current guidelines recommend limiting saturated fat to 7% of energy intake, but careful consideration should be given to the replacing macronutrient and overall dietary pattern (Tables 27.1 and 27.2).

Polyunsaturated fat

The most abundant PUFA in the diet is linoleic acid, which is inversely associated with diabetes incidence and cardiovascular disease in prospective cohort studies [90, 92]. The use of long-chain PUFAs as biomarkers for intake strengthens the subjective nature of cohort studies, which typically rely on self-reported dietary intake [90, 104]. Clinical trials evaluating the effect of PUFAs on insulin sensitivity or surrogate markers for diabetes risk have not been consistent [105–107]. The short duration of some of these studies may be important, as PUFAs are believed to act partly via altering membrane fluidity, which may take up to three months [90].

Replacement of saturated fat with PUFAs reduces cardiovascular disease risk, and surrogate risk markers [97–101, 108, 109], and sources of PUFAs such as nuts, seeds, and vegetable oils should be encouraged as part of a healthy diet (Tables 27.1 and 27.2).

Omega-3 fatty acids

There is little evidence from observational and experimental studies that omega-3 fats improve glycaemia in healthy individuals and people with type 2 diabetes [110, 111] or reduce the risk of developing diabetes [107], and high doses of fish oil impair glucose homeostasis [110]. In contrast, the cardioprotective effects of omega-3 fats, such as reducing serum triglycerides and modifying platelet aggregation and thrombogenicity [112], have led to recommendations to include oily fish twice a week to reduce cardiovascular disease [2, 33, 113]. Importantly, *more* is not better, and previous support for omega-3 supplementation for prevention of cardiovascular disease in people with diabetes was withdrawn by NICE [33].

Monounsaturated fat

Recent evidence from the PREDIMED (Prevención con Dieta Mediterránea) and earlier KANWU (Kuopio, Aarhus, Naples, Wollongong and Uppsala) trials suggests MUFAs may improve insulin sensitivity and reduce diabetes risk independent of energy restriction, particularly where MUFAs replace SFAs [93, 114]. There is also good evidence from randomized controlled trials that diets high in MUFAs can reduce glucose concentrations in people with type 2 diabetes [115–117], and can be used to replace carbohydrate without detrimental effects [2, 118]. There are few studies that have specifically examined the effect of MUFAs on glycaemic levels in individuals with type 1 diabetes, and there is insufficient evidence to make firm recommendations.

Replacing SFAs with MUFAs can reduce risk of cardiovascular disease [119, 120], and controlled trials demonstrate that high-MUFA diets can increase HDL cholesterol, lower blood pressure, and improve other surrogate markers of cardiovascular disease risk [98, 105, 108, 121, 122].

MUFA is a significant component of a Mediterranean diet [123], and it is important to consider the confounding effects on clinical risk factors of other aspects of this dietary pattern, including fish, fruits and vegetables, and moderate alcohol. For example, in the PREDIMED trial, extra-virgin olive oil had a greater effect on cardiovascular disease risk reduction than olive oil, despite identical proportions of MUFA, indicating that nutritive and non-nutritive components are also important [124]. Therefore, while MUFAs appear to have independent effects on glucose homeostasis and cardiovascular disease risk, greater risk reduction is likely achieved by following a diet rich in wholegrains, fruit, vegetables, fish, and limited saturated fat [2, 123, 124].

Trans fats

Trans fats occur naturally in foods such as milk or other dairy products as a byproduct of rumination or are produced industrially (partially hydrogenated vegetable oils). There is little evidence that total trans fat in the diet influences glucose homeostasis [125]; however, prospective studies using the dairy fat transpalmitoleic acid as a biomarker have shown that this naturally occurring trans fat is inversely related to diabetes risk [126]. However, it is unclear whether the fat *per se* has beneficial effects on glucose homeostasis, or whether the erstwhile nutrients of dairy mediate this risk reduction. Naturally occurring trans fats are found in minute amounts in dairy foods, whereas industrially produced trans fat can contribute up to 4 g a day in US diets [127].

There is compelling evidence from clinical and epidemiological studies that industrially produced trans fats have a deleterious effect on cardiovascular disease risk [127–129], and national and international guidelines have recommended their reduction or complete elimination in the diet [2, 127, 130].

In practice, these observations support and inform recommendations for a healthy dietary pattern (Table 27.2), with dairy products forming part of approaches, such as the well-researched Dietary Approaches to Stop Hypertension (DASH) diet, and minimizing foods high in hydrogenated vegetable oil, which typically include biscuits, cakes, and other sweet, high-fat goods.

Dietary cholesterol

There is little evidence that dietary cholesterol increases diabetes risk [131]. Instead, recommendations to limit cholesterol intake come from some clinical studies, which have demonstrated that dietary cholesterol can raise LDL cholesterol [132]. This contention has been a subject of considerable debate for many years. A recent meta-analysis of prospective studies examining whether dietary cholesterol ultimately influences risk of cardiovascular disease was inconclusive [133] and the American Heart Association/American

College of Cardiology have raised concerns about the heterogeneity of the data available [127]. However, given the potential impact of dietary cholesterol on LDL cholesterol, the possible increased absorption of dietary cholesterol in people with diabetes [134], and the elevated risk of cardiovascular disease in people with diabetes, any changes to current guidelines to limit dietary cholesterol to 200–300 mg/d are premature [135].

Protein

Given the primary role of weight loss in the prevention and management of type 2 diabetes and prevention of cardiovascular disease, numerous studies have evaluated the effect of higher protein intakes on satiety and weight management in amounts of up to 40% energy from protein [136–139]. However, the concomitant changes in the amount and quality of carbohydrate and fat in these studies make it difficult to draw any firm conclusions. Guidelines therefore reiterate that the most effective weight loss diet is one that takes into account an individual's preferences, beliefs, cultural values, and practical considerations [1, 2, 140].

Protein is also a macronutrient of interest due to its capacity to increase insulin secretion acutely [141]. However, a high protein intake could induce insulin resistance [142], and therefore the long-term effect of high protein on glycaemia [143] or type 2 diabetes risk may be a trade-off between its effect on promoting prandial insulin release while potentially reducing insulin sensitivity [144]. Suggestions that dietary protein may be modestly linked to increased risk of diabetes [145] may reflect sources of protein such as red or processed meats; dietary patterns that provide vegetable sources of protein alongside low-fat meat represent a prudent approach (Table 27.1).

Increasing the protein content of the diet lowers liver fat [146, 147], independent of weight loss. The provision of amino acids protects against hepatic triglyceride deposition under experimental obesogenic conditions [148, 149]. Given the association between liver fat and type 2 diabetes, high-protein diets might therefore be expected to offer protection against the development of type 2 diabetes.

High-protein diets may also have a role to play in managing hypertension. Observational studies [150] and trials in which carbohydrate is replaced with protein [151, 152] indicate that diets high in plant-based protein in particular may help in managing this cardiovascular disease risk factor.

People with diabetes are at higher risk of renal disease, and caution should be employed when recommending changes to protein intake in individuals with chronic kidney disease. In people with stage 3–5 chronic kidney disease not requiring dialysis, a restricted protein intake of 0.6–0.8 g/kg of body weight/d has been recommended by expert panels [153]. Persons with chronic kidney disease on dialysis require 1.0–1.2 g/kg of body weight/d [153].

Micronutrients

Several micronutrients have been specifically linked to diabetes risk in cohort studies; however, very few randomized controlled trials have confirmed these associations. Such micronutrients include magnesium [154], vitamin D [155], calcium [156], and chromium [157]. Similarly, epidemiological trials and *in vitro* data have suggested that antioxidant vitamins and folate (vitamins A, C, E, and beta-carotene) could play a role in modifying cardiovascular disease risk. However, well-designed randomized controlled trials to confirm these associations are lacking [158], and NICE does not recommend such supplementation [159].

Therefore, current guidelines recommend regular consumption of a variety of vegetables, fresh fruit, legumes, dairy products, vegetable oils, nuts, wholegrain breads, and oily fish to ensure that recommended vitamin and mineral requirements are met [1] (Tables 27.1 and 27.2). This message should be reinforced alongside clarification that there is no proven benefit of vitamin or mineral supplements for management of diabetes.

Salt or sodium

Reduced sodium intake can lower blood pressure, and sodium intake should be limited across the population, including individuals at higher risk of cardiovascular disease [160, 161]. A reduction in mean salt intake of 3 g/d for adults (to achieve a target of 6 g/d) would lead to around 14–20 000 fewer deaths per year from cardiovascular disease [162]. Dietary patterns, such as the DASH diet, that are low in sodium and high in potassium, magnesium, and calcium form an effective approach to control hypertension and are appropriate in people with diabetes (Table 27.2).

Sterols and stanols

Plant sterols and stanols have no known effect on glucose homeostasis, but reduce LDL and total cholesterol in people with and without diabetes [163]. Dietary guidelines have recommended 2–3 g/d of fortified foods to lower LDL and total cholesterol irrespective of whether the individual is taking statins [2], but they are not included in the updated NICE guidelines for lipid modification in the prevention of cardiovascular disease in people with diabetes.

Alcohol

In cross-sectional and prospective studies, a modest alcohol intake is associated with a reduced risk of diabetes and cardiovascular disease, while excessive (>30–60 g/d) and chronic intakes appear to raise blood pressure, increase plasma triglycerides, and heighten the risk of cardiovascular disease [164, 165].

In people with diet-treated diabetes, alcohol consumed with carbohydrate may raise glucose levels, but does not appear to affect glucose or insulin concentrations when consumed alone [140]. However, in people treated with insulin or insulin secretagogues, alcohol increases the risk of hypoglycaemia [2, 140]. The risk increases with the quantity of alcohol consumed and may remain elevated the following day [166]. Therefore, in these people, alcohol should be consumed with food.

Finally, alcohol is a source of energy and is associated with increases in BMI and greater waist-to-hip ratio [167]. Therefore, recommendations for prevention and management of diabetes are the same as those for the general population: 2–3 units/d in women;

3–4 units/d in men [2]. One alcohol unit is measured as 10 ml or 8 g of pure alcohol. This equals one 25 ml single measure of whisky (alcohol by volume [ABV] 40%), or a third of a pint of beer (ABV 5–6%), or half a standard (175 ml) glass of red wine (ABV 12%). The new UK Department of Health guidelines recommended only 14 units per week for both men and women [168].

Diet in special circumstances

Diet in pregnancy

Diabetes increases the risk of adverse pregnancy outcomes, and the risk increases with the duration of diabetes (Chapter 71) [169]. Maintenance of HbA_{1c} towards the target of 48 mmol/mol (6.5%) is likely to reduce the risk of congenital malformations, but may be associated with increased episodes of hypoglycaemia. Excess weight gain is associated with worse glycaemic levels [140, 170]. Therefore, women with a BMI of 27 kg/m^2 should be provided with advice and support to attain a healthy weight prior to pregnancy [170]; however, weight reduction should not be attempted during pregnancy [171]. In the UK there are no specific guidelines on weight gain during pregnancy, though NICE emphasizes that energy needs do not change in the first six months of pregnancy and increase by a modest degree (approximately 200 kcal/d) in the last three months. The Institute of Medicine has more defined guidelines for weight gain over each trimester, which range from 11 to 20 lb (5–9 kg) for mothers who have obesity at conception to 28–40 lb (13–18 kg) for underweight mothers [172]. There is little evidence to support particular dietary approaches during pregnancy. However, a low-GI diet may modestly improve glycaemia [2, 173].

Folic acid requirements increase to 5 mg/d for women with diabetes, as risk of neural tube defects is increased [168]. Folic acid should be taken up to 12 weeks' gestation to prevent neural tube defects. However, in practice, 50% of pregnancies in the UK are unplanned, in which case folic acid supplementation should be commenced immediately [168].

Diet in children with diabetes

Management of type 1 diabetes and type 2 diabetes in children does not differ substantively from that in adults [140, 174, 175]. Children and their families (or carers) should receive education that covers insulin therapy and dosage adjustment; blood glucose monitoring; detecting and managing hypoglycaemia, hyperglycaemia, and ketosis; and the effects of diet, physical activity, and intercurrent illness on blood glucose levels. Additionally, age and maturity, emotional well-being, and life goals should be considered in an individualized approach. As energy requirements change with age, growth rates have to be monitored and the evaluation of a meal plan should be rechecked at least once a year [176].

As in all healthy children, energy and nutrient intakes should be adequate to ensure optimal growth and development. Good nutrition may also contribute to maintaining normal serum lipid values and meeting blood pressure goals. Meal plans must be individualized to accommodate food preferences and the eating pattern of the family [176].

Exercise and insulin-treated diabetes

Physical activity and exercise have numerous benefits for people with diabetes, including improved glucose levels, lower blood pressure, reduced requirements for medications, and lower cardiovascular risk (Chapter 28) [1–3]. However, risk of hypoglycaemia increases with exercise intensity and duration in insulin-treated diabetes, and careful management of glucose is critical [1–3, 177]. Referral to a specialist diabetes dietitian is recommended to advise on optimal management of different modalities, duration, and intensity of exercise [3]. However, general recommendations for insulin-treated diabetes are to adjust insulin dosing for planned exercise, and to provide additional dietary carbohydrate for unplanned exercise [2, 50, 177]. In practice, for the majority of people who engage in moderate physical activity, additional carbohydrate requirements increase only modestly, and an additional 10–15 g/h should be sufficient to maintain blood glucose levels [50].

For more serious exercisers and athletes, the amount of carbohydrate required will be based on the individual, with sufficient carbohydrate prior to exercise in order to maintain glucose levels during the exercise, and replenishment of glycogen stores in the post-exercise period to enhance performance and prevent hypoglycaemia during the next exercise bout, particularly for those who exercise daily [175, 178]. The complexity, both physiological and psychological, of managing glycaemia during exercise has been acknowledged, and individuals with type 1 diabetes may benefit from specialist support [179].

Many exercisers, particularly young men engaged in weight training, have specific questions about protein intake. There is little evidence that excessive protein intake increases muscle growth or mass in most casual exercisers; but for weight lifters or endurance athletes, the American College of Sports Medicine recommends 1.4–1.7 g/kg/d [180, 181]. In general, most athletes or weight-training men will meet this protein requirement through diet alone. For individuals who do not consume sufficient protein, shakes supplemented with proteins such as whey can be consumed. However, careful monitoring of blood glucose is advised, as whey and other proteins lower glucose levels in people with and without diabetes [147, 182]. Although no studies have been carried out in people with type 1 diabetes, whey could theoretically increase the risk of post-exercise hypoglycaemia. In practice, most shakes of this type will contain additional carbohydrate, which may counteract any glucose-lowering effect.

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28 Physical Activities and Diabetes

Emma J. Cockcroft[1] and Robert C. Andrews[2,3]

[1] Faculty of Health & Life Science, Department of Health and Community Sciences, University of Exeter, Exeter, UK
[2] Faculty of Health & Life Science, Clinical and Biomedical Sciences, University of Exeter, Exeter, UK
[3] Department of Diabetes, Taunton and Somerset NHS Foundation Trust, Taunton, UK

Key points

- In people with type 1 diabetes, exercise improves fitness and strength, reduces cardiovascular risk factors, and improves well-being.
- While regular exercise has not conclusively been found to improve glycaemia in type 1 diabetes, it is associated with decreased long-term morbidity and mortality in this population.
- Managing type 1 diabetes in the context of exercise can be complicated by both hypoglycaemia and hyperglycaemia during and after exercise.
- It is recommended that individuals with type 1 diabetes adjust their insulin dose and carbohydrate consumption prior to, during, and/or after exercise to accommodate the type, intensity, and duration of exercise performed.
- Structured, supervised diet and exercise interventions can reduce the risk of developing type 2 diabetes by ~60% in individuals with impaired glucose tolerance.
- Regular exercise improves fitness and strength, reduces cardiovascular risk factors, and improves glycated haemoglobin (HbA_{1c}), and is associated with decreased long-term morbidity and mortality in people with type 2 diabetes.
- People with type 2 diabetes should combine aerobic and resistance exercises for ≥150 min/wk to maximize the effect of exercise on glucose levels.
- While regular exercise has not conclusively been found to prevent gestational diabetes, there is emerging evidence that it can improve glycaemia in women with gestational diabetes.

Defining exercise, type of exercise, and intensity

Physical activity, exercise, and physical fitness are terms that describe different concepts. However, they are often confused with one another, and the terms are sometimes used interchangeably. Physical activity is defined as any bodily movements that involve muscle contraction to produce energy expenditures above the basal level. Exercise is a type of physical activity, which is planned, structured, and repetitive, with the objective of improving or maintaining physical fitness [1]. Physical fitness is generally accepted as the ability to carry out daily tasks without undue fatigue. Physical fitness comprises various elements, including health-related and skill-related components.

Physical activity is measured in metabolic equivalent (MET) units that estimate the oxygen consumption of an activity. One MET is equivalent to oxygen consumption of 3.5 ml O_2/kg/min in a resting seated adult. Moderate physical activity, which includes leisure cycling, swimming, walking, and general house cleaning, is equivalent to 3–6 METs. Vigorous physical activity is activities equivalent to >6 METs, such as running, rope jumping, and sit-ups.

Physical fitness refers to the circulatory and respiratory systems' ability to supply oxygen during sustained exercise. The intensity of an exercise is typically measured as a percentage of maximal oxygen consumption (VO_{2max}). Moderate activity is when the body utilizes 40–60% of VO_{2max}, whereas high-intensity activity reaches 80–90% VO_{2max}. The volume of exercise is usually measured by the duration of the activity.

Exercise can be categorized into aerobic, anaerobic and resistance training. There are few data to support that one type of exercise is superior to another in terms of general health benefits [2]. However, an exercise that is enjoyable and suitable to the individual is likely to be performed regularly and maintained for a longer period.

Aerobic exercise engages large muscle groups with repetitive and continuous movements for ≥10 minutes to produce improved oxygen utilization with the aim of improving cardiovascular and respiratory fitness. Examples include walking, cycling, and jogging.

Anaerobic exercise comprises short, but high-intensity, bursts of physical activity that rely on rapid release of energy produced via glycolysis, rather than being dependent on oxygen consumption. This exercise builds lean muscles, improves muscle and bone strength, and enhances sports performance.

Resistance training enhances muscle strength by working muscles against a resistance load or weight. By altering the combination of weight load and frequency of repetition, this exercise improves muscle endurance and strength as well as increasing the lean muscle mass and metabolic rate.

Aerobic, anaerobic, and resistance training exercises can be used alone or in combination to achieve the desired effect of improving cardiorespiratory fitness, muscle strength, and endurance, as well

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as achieving weight loss and its maintenance. The type, intensity, and volume of exercise should be tailored to individual needs to allow maximal adherence and long-term health benefits. Although the benefits greatly outweigh the risks, there are restrictions to exercise for people with certain medical conditions in terms of the type and intensity of physical activity. Gradual increases in exercise intensity and volume are generally advisable, but especially in those who are ordinarily sedentary at the start of an exercise programme.

Type 1 diabetes and exercise

Prevention of type 1 diabetes

Many people view type 1 diabetes as affecting young, otherwise healthy individuals. This together with the disease's autoimmune pathogenesis mean that regular exercise is not typically thought to prevent type 1 diabetes. Evidence is now emerging, however, that exercise may be one of the modifiable factors that interact with genetic predisposition to determine if and when type 1 diabetes develops [3].

Figure 28.1 shows the possible mechanism by which exercise could improve or maintain β-cell mass. Physical activity induces elevations in circulating levels of growth hormone (GH), insulin-like growth factor I (IGF-I), glucagon-like peptide 1 (GLP-1), interleukin 6 (IL-6), and IL-1 receptor agonist (IL-1 RA), all of which increase proliferation of β cells [4–8]. By reducing fat and visceral fat mass, exercise reduces pro-inflammatory adipokines, such as leptin and tumour necrosis factor α (TNF-α), and increases anti-inflammatory adipokines, such as adiponectin, which may help to reduce β-cell death [9]. Exercise may reduce the destructive immune response to the β cell by reducing the Toll-like receptors (TLRs) on monocytes and macrophage immune cells [10]. Finally, exercise improves insulin sensitivity, which in turn helps to normalize plasma glucose [11] and serum lipids [12], which may cause β-cell death when chronically elevated.

In animal models of diabetes, exercise protects the β cell from oxidative stress [13]. In healthy individuals [14], those at risk of type 2 diabetes [15], and people with type 2 diabetes, regular exercise improves β-cell function [16]. However, no human studies have examined whether exercise can delay or prevent individuals at risk from type 1 diabetes from developing the disease. However, the fact that exercise improves insulin resistance, which predicts progression to type 1 diabetes [17], coupled with findings from a cross-sectional study that reported that increased physical activity was associated with better glucose levels, lower insulin needs, and higher C-peptide levels at the onset of type 1 diabetes [18], suggests that more human research is needed in this area.

Treatment of type 1 diabetes

Although the evidence for benefit is less than for type 2 diabetes, there is sufficient to suggest that exercise should be encouraged in people with type 1 diabetes. Figure 28.2 summarizes the benefits that people with type 1 diabetes can expect from exercise.

Physical fitness, cardiovascular disease, and mortality

Although there are only a few small studies of fitness in people with type 1 diabetes, young adults (12–44 years old) with type 1 diabetes are less fit than matched individuals without diabetes, despite similar levels of physical activity [20–24]. Abnormalities in cardiac muscle and autonomic nerve function [25], reduction in skeletal muscle size and power [26], as well as an altered cardiac metabolism that favours non-esterified fatty acids (NEFA) over glucose as a fuel source [27], may contribute to this. Supervised physical activity programmes, however, improve fitness in people with type 1 diabetes [28–30], with increases in VO_{2max} of up to 27% [22, 30–34].

No large randomized controlled trials (RCTs) have examined whether regular physical activity reduces cardiovascular disease or mortality in type 1 diabetes. A large retrospective study, the Pittsburgh Insulin-Dependent Diabetes Mellitus (IDDM) Morbidity and Mortality study, suggests that regular physical activity may be of benefit. This study demonstrated that in men with

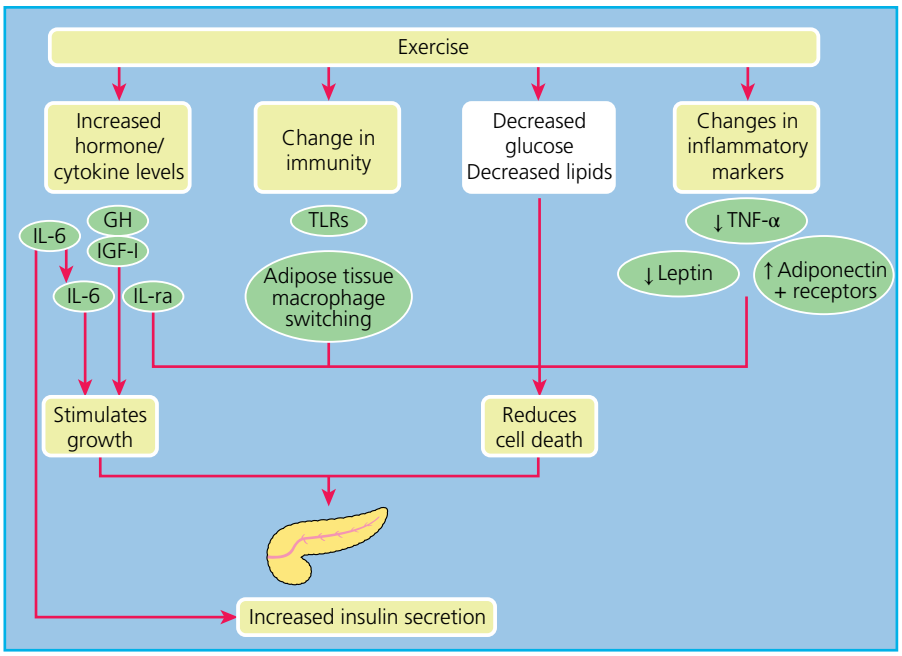

Figure 28.1 Potential mechanisms through which exercise could improve β-cell mass and/or function. GH, growth hormone; GLP-1, glucagon-like peptide 1; IGF-I, insulin-like growth factor I; IL-ra, interleukin 1 receptor agonist; IL-6, interleukin 6; TLR, Toll-like receptors; TNF-α, tumour necrosis factor α. Source: Reproduced with permission from Narendran et al. 2015 [3].

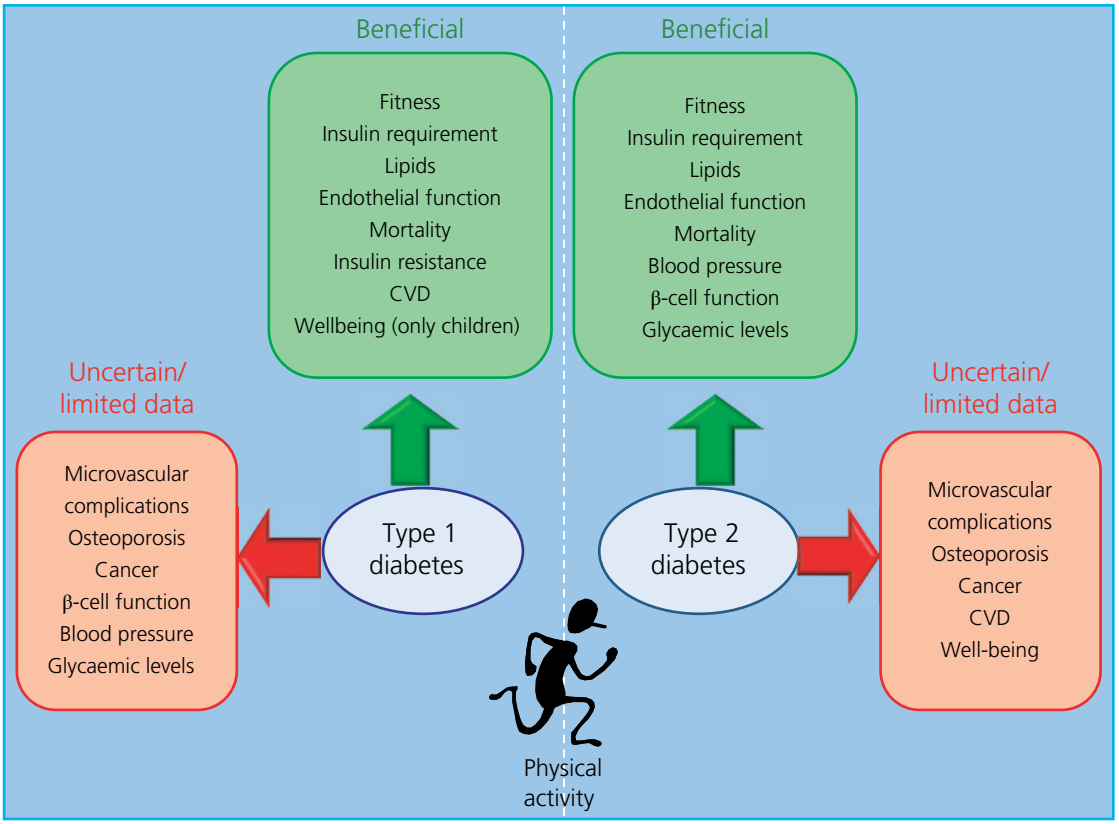

Figure 28.2 Health benefits of physical activity in type 1 diabetes and type 2 diabetes. CVD, cardiovascular disease. Source: Chimen et al. 2011 [19]. Reproduced with permission from Springer.

type 1 diabetes of 25 years' duration, those who had participated in team sports during high school were three times less likely to report macrovascular disease and had mortality rates three times lower than those who did not participate [35]. This pattern was not seen in women, but their participation in team sports was lower (24% reported participation versus 39% in men). The level of physical activity in adulthood (measured using a validated questionnaire) also predicted mortality at six years [20]. Sedentary men were three times more likely to die than active men, and a similar (but again non-significant) effect was seen in women. In the Finnish Diabetic Nephropathy (FinnDiane) study, a prospective and observational study of 2369 individuals with type 1 diabetes who were followed up for a mean of 11.4 ± 3.5 years, exercise was associated with a lower risk of premature all-cause and cardiovascular mortality in both men and women with type 1 diabetes. This study also demonstrated that physical activity is associated with a lower risk of mortality in those with type 1 diabetes and chronic kidney disease [36].

Glycaemic levels and insulin requirements

The effect of physical activity on glycaemia in people with type 1 diabetes is unclear, with some studies showing benefit but the majority showing no benefit. Table 28.1 lists the intervention studies where the controls have type 1 diabetes and Table 28.2 lists other studies.

The intervention studies have tended to use supervised exercise programmes of short duration (1–3 months), have involved small numbers of participants (all but one had fewer than 60), and predominantly involved adolescents or young adults. There have been several meta-analyses of the effect of exercise on glycated haemoglobin (HbA_{1c}) in type 1 diabetes. Kennedy et al. only included studies in which there was a non-intervention group of participants with type 1 diabetes [80]. They found no glycaemic benefit of exercise in people with type 1 diabetes. However, subanalyses suggested that exercise may confer glycaemic benefit in the young, and when undertaken for longer periods. They also stated that exercise can be carried out by people with type 1 diabetes without significant risk of hypoglycaemia. This is important because some studies have reported that hypoglycaemia is a barrier to exercise in those with type 1 diabetes [81, 82].

Tonoli et al. [83] used less stringent criteria, including trials with no control groups, but excluded some of the studies used in the Kennedy analysis. Exercise overall resulted in a small but statistically significant reduction in HbA_{1c} (0.3%; 3 mmol/mol). When exercise was analysed by type, aerobic exercise reduced HbA_{1c} by 0.2% (2 mmol/mol), strength training did not lower HbA_{1c}, and combined aerobic exercise and strength training showed a statistically significant reduction in HbA_{1c} of −1.6% (17 mmol/mol).

In the meta-analysis by Wu et al. [84], studies were included if they were RCTs, quasi-experimental trials, and crossover trials and the exercise intervention comprised supervised or unsupervised aerobic, resistance, or combined physical activity for ≥4 weeks. The study identified 21 studies that met these criteria and had HbA_{1c} before and after the intervention, with 7 having adult participants and 17 children and adolescents. Overall HbA_{1c} fell by 0.45% (5 mmol/mol) in the exercise group compared to control. When broken down by age, children and adolescents saw a fall of 0.6% (6 mmol/mol), but no effect was seen in adults. Subgroup analysis showed that combined exercise was the only form of exercise that

Table 28.1 Intervention studies evaluating the effect of physical activity on glycated haemoglobin (HbA_{1c}) in people with type 1 diabetes.

						Type 1 diabetes control group		Type 1 diabetes intervention group	
Study	**n (Control/type 1 diabetes)**	**Mean age ± SD/age range (years)**	**RCT (yes/no)**	**Duration**	**Type of physical activity**	**HbA_{1c} before (%) (mmol/mol)**	**HbA_{1c} after (%) (mmol/mol)**	**HbA_{1c} before (%) (mmol/mol)**	**HbA_{1c} after (%) (mmol/mol)**
No HbA_{1c} effect									
Yki-Jarvinen et al. [30]	6/7	NA	No	6 wk	Supervised aerobic physical activity	8.6 ± 0.4 (70 ± 5)	8.6 ± 0.4 (70 ± 5)	8.6 ± 0.4 (70 ± 5)	8.6 ± 0.4 (70 ± 5)
Landt et al. [32]	6/9	14–16	No	12 wk	Supervised aerobic physical activity	12 ± 1 (108 ± 11)	12 ± 1 (108 ± 11)	12 ± 1 (108 ± 11)	12 ± 1 (108 ± 11)
Wallberg-Henriksson et al. [34]	7/6	25–45	No	5 mo	Non-supervised aerobic physical activity	10.6 ± 0.6 (92 ± 7)	10.4 ± 0.6 (90 ± 7)	10.4 ± 0.6 (90 ± 7)	10.5 ± 0.6 (91 ± 7)
Huttunen et al. [37]	16/16	8.2–16.9	No	3 mo	Supervised aerobic physical activity	9.4 ± 2.1 (79 ± 23)	9.7 ± 2.2 (83 ± 24)	9.8 ± 2.3 (84 ± 25)	10.5 ± 2.5 (91 ± 28)
Laaksonen et al. [28]	28/28	32.5 ± 5.7	Yes	12–16 wk	Supervised aerobic physical activity	8.2 ± 1.1 (66 ± 12)	8.2 ± 1.0 (66 ± 11)	8.3 ± 1.3 (67 ± 14)	8.5 ± 1.6 (69 ± 18)
Fuchsjager-Mayrl et al. [31]	8/18	42 ± 10	No	4 mo	Supervised aerobic physical activity	7.4 ± 0.4 (57 ± 6)	7.2 ± 0.2 (55 ± 2)	7.3 ± 0.2 (56 ± 2)	7.5 ± 0.3 (58 ± 4)
Newton et al. [38]	40/38	14 ± 2	Yes	12 wk	Non-supervised aerobic physical activity	8.5 ± 2.8 (69 ± 31)	8.5 ± 2.8 (69 ± 31)	8.0 ± 1.8 (64 ± 20)	8.3 ± 1.8 (67 ± 20)
D'Hooge et al. [39]	8/8	10–17	Yes	20 wk	Supervised aerobic and resistance training	8.8 ± 2.0 (73 ± 22)	8.6 ± 2.2 (71 ± 24)	7.9 ± 2.5 (63 ± 27)	7.8 ± 2.4 (62 ± 26)
Wong et al. [40]	11/12	12 ± 3	Yes	3 mo	Home-based aerobic exercise	8.3 ± 1.4 (67 ± 16)	8.3 ± 1.3 (67 ± 14)	8.1 ± 1.0 (65 ± 11)	8.2 ± 1.0 (66 ± 9)
Tunar et al. [41]	14/17	14 ± 2	Yes	3 mo	Supervised Pilates class	8.9 ± 1.6 (74 ± 17)	8.8 ± 1.5 (73 ± 16)	9.2 ± 2.1 (77 ± 23)	8.7 ± 1.8 (72 ± 19)
Brazeau et al. [42]	23/25	45 ± 14	Yes	12 mo	Non-supervised aerobic physical activity	7.9 ± 1.0 (63 ± 10)	7.9 ± 1.1 (63 ± 12)	8.1 ± 1.3 (65 ± 14)	8.2 ± 1.2 (66 ± 13)
Narendran et al. [43]	28/30	32 ± 11	Yes	12 mo	Non-supervised aerobic physical activity	9.0 ± 4.4 (75 ± 50)	7.3 ± 2.4 (56 ± 27)	9.0 ± 4.4 (75 ± 50)	7.4 ± 2.4 (56 ± 28)
Gusso et al. [44]	15/38	16 ± 1	Yes	20 wk	Supervised aerobic physical activity	8.6 ± 1.5 (70 ± 16)	8.7 ± 1.2 (71 ± 13)	8.8 ± 2.2 (73 ± 16)	8.5 ± 1.1 (69 ± 13)
Mohammed et al. [45]	10/10	9–13	Yes	12 wk	1.5 hr of football twice per week	10.5 ± 2.4 (91 ± 27)	11.0 ± 2.1 (97 ± 23)	11.5 ± 2.7 (102 ± 30)	11.2 ± 2.3 (99 ± 25)
HbA_{1c} improvement									
Dahl-Jorgensen et al. [46]	8/14	5–11	No	5 mo	Supervised aerobic physical activity	13.4 ± 1.9 (123 ± 21)	12.9 ± 1.6 (117 ± 18)	15.1 ± 2.2 (142 ± 49)	13.8 ± 1.9 (127 ± 21)
Campaigne et al. [47]	9/10	9 ± 0.47	Yes	12 wk	Supervised vigorous physical activity	13.9 ± 0.61 (128 ± 8)	13.3 ± 0.54 (122 ± 6)	12.5 ± 0.65 (113 ± 7)	11.3 ± 0.5 (100 ± 5)
Stratton et al. [48]	8/8	15 ± 1	Yes	8 wk	Supervised aerobic physical activity	11.7 ± 2.9 (104 ± 32)	11.4 ± 2.9 (101 ± 32)	10.1 ± 2.2 (87 ± 23)	9.9 ± 2.2 (85 ± 23)

(*continued*)

Table 28.1 (*Continued*)

Study	n (Control/type 1 diabetes)	Mean age ± SD/age range (years)	RCT (yes/no)	Duration	Type of physical activity	Type 1 diabetes control group		Type 1 diabetes intervention group	
						HbA_{1c} before (%) (mmol/mol)	HbA_{1c} after (%) (mmol/mol)	HbA_{1c} before (%) (mmol/mol)	HbA_{1c} after (%) (mmol/mol)
Durak et al. [49]	8/8 (crossover)	31 ± 3.5	Yes	10 wk	Supervised heavy resistance training	6.9 ± 1.4 (52 ± 15)	6.9 ± 1.4 (52 ± 15)	6.9 ± 1.4 (52 ± 15)	5.8 ± 0.9 (40 ± 10)
Perry et al. [50]	30/31	20–69	Yes	6 mo	Non-supervised aerobic physical activity	8.7 ± 2.0 (72 ± 21)	8.8 ± 2.3 (73 ± 25)	8.9 ± 2.6 (74 ± 28)	8.6 ± 2.1 (70 ± 23)
Salem et al. [51]	48/Moderate 75/ Intensive 73	14.5 ± 2.4	Yes	6 mo	Supervised aerobic and resistance physical activity	8.3 ± 2.1 (67 ± 23)	8.9 ± 1.4 (74 ± 15)	Moderate: 8.9 ± 1.4 (74 ± 15) Intensive 8.9 ± 1.6 (74 ± 17)	Moderate: 8.1 ± 1.1 (65 ± 12) Intensive 7.8 ± 1.0 (62 ± 11)
Aouadi et al. [52]	11/11 two times per week/11 three times per week	12–14	No	6 mo	Supervised aerobic physical activity	9.5 ± 2.5 (80 ± 38)	9.7 ± 1.1 (83 ± 12)	Two times per week 8.6 ± 2.2 (71 ± 24) Four times per week 8.2 ± 1.5 (66 ± 17)	Two times per week 8.2 ± 1.3 (66 ± 14) Four times per week 6.8 ± 1.1 (51 ± 12)
Lee et al. [53]	15/15	44 ± 10	Yes	12 wk	High-intensity interval training	8.4 ± 0.7 (68 ± 8)	8.2 ± 1.0 (67 ± 10)	8.6 ± 0.7 (71 ± 7)	8.1 ± 1.0 (65 ± 11)
Petschnig et al. [54]	14/15	9–13	Yes	32 wk	Supervised strength training	7.8 ± 1.4 (62 ± 14)	8.7 ± 1.3 (72 ± 14)	8.8 ± 1.4 (72 ± 14)	8.0 ± 1.3 (64 ± 14)

All studies quoted have included people with type 1 diabetes in both the intervention and control groups. The studies are listed in chronological order according to whether or not physical activity improved HbA_{1c}.
RCT, randomized controlled trial; SD, standard deviation.
Source: Adapted with permission from Chimen et al. 2011 [19].

Table 28.2 Interventional and observational studies evaluating the effect of physical activity on glycated haemoglobin (HbA_{1c}) in people with type 1 diabetes.

Study	n (Type 1 diabetes)	Mean age (years)	Design	Duration	Type of exercise	VO_{2max}	HbA_{1c} before (%, mmol/mol)	HbA_{1c} after (%, mmol/mol)
No HbA_{1c} effect								
Wallberg-Henriksson et al. [27]	9	NA	Case series	16 wk, 1 h, 2–3 times/wk	Aerobic exercise: jogging, running, ball games, and gymnastics	↗ 8%	10.4 ± 0.7 88 ± 8	11.3 ± 0.5 97 ± 5
Wallberg-Henriksson et al. [55]	10	NA	Control trial	8 wk, 45 min, 3 times/wk	Aerobic exercise: running	↗ 13%	NA	NA
Zinman et al. [56]	13	30 ± 1.8	Control trial	12 wk, 45 min, 3 times/wk	Aerobic exercise: cycling	↗ 8%	10.7 ± 0.3 91 ± 3	10.3 ± 0.8 87 ± 9
Baevre et al. [57]	6	14 to 17	Case series	6 mo	Aerobic exercise	NA		
Selam et al. [58]	50	NA	Cross-sectional study	Weekly energy expenditure	Total physical activity index (questionnaire)	NA	NA	NA
Lehmann et al. [59]	20	NA	Case series	3 mo, ≥135 min/wk	Endurance training	↗	7.6 60	NA
Ligtenberg et al. [60]	221	31.7	Cross-sectional study	Measurement of physical activity for past year	Total physical activity index (questionnaire)	NA	No correlation between total physical activity and HbA_{1c}	NA
Rigla et al. [61]	14	25.5 ± 6	Case series	3 mo, 1 h min, 3 times/wk	Aerobic activity at 60–75% VO_{2max}: treadmill, bicycle	↗ 5%	6.5 ± 0.8 48 ± 9	6.7 ± 1 50 ± 11
Rigla et al. [61]	14	25.5 ± 6	Control trial	3 mo, 1 h, 3 times/wk	Aerobic exercise: running, cycling	↗	6.5 ± 0.8 48 ± 9	6.7 ± 1 50 ± 11
Roberts et al. [62]	24	Adolescent	Case series	24 wk	Supervised training	↗ 17% in aerobic capacity	NA	NA
Sarnblad et al. [63]	26	15.7 ± 2.1	Cohort study	7 days	Measurement of physical activity	NA	No association between time spent exercising and HbA_{1c}: 7.6 ± 1.4 60 ± 15	NA
Mittermayer et al. [64]	11	44 ± 3	Control trial	4 mo, 50 min, 2–3 times/wk	Supervised aerobic exercise: cycling	NA	7.2 ± 0.2 55 ± 2	7.6 ± 0.3 59 ± 3
Haider et al. [65]	18	42 ± 10	Control trial	4 mo, 1 h, 2–3 times/wk	Supervised aerobic exercise	NA	7.3 ± 0.9 56 ± 10	7.5 ± 1 58 ± 11
Ramalho et al. [66]	13	13–30	Case series	12 wk, 40 min, 3 times/wk	Aerobic vs resistance	NA	Aerobic: 8.7 ± 1.6 71 ± 17 Resistance: 8.2 ± 2.9 66 ± 31	Aerobic: 9.8 ± 1.8 84 ± 19 Resistance: 7.6 ± 1.6 59 ± 17
Harmer et al. [67]	8	25 ± 4	Control trial	7 wk, 3 times/wk	Supervised aerobic exercise: intense cycling	NA	8.6 ± 0.8 70 ± 9	8.1 ± 0.6 65 ± 7
Aman et al. [68]	NA	11–18	Cross-sectional study	NA	Measurement of leisure time activity	NA	No association of physical activity	NA
Edmunds et al. [69]	46	12.8 ± 2.1	Cross-sectional study	Measurement of physical activity for 2 weeks	Moderate and vigorous activity (questionnaire)	NA	No association between time spent exercising and HbA_{1c}	NA
Minnebeck et al. [70]	11 11	41 ± 14 42 ± 15	Cohort study 11 BMI 29 ± 2 kg/m^2 11 BMI 23 ± 1 kg/m^2	4 wk	High-intensity interval training	NA	7.5 ± 0.5 58 ± 5 7.3 ± 0.9 56 ± 10	7.3 ± 0.4 56 ± 4 7.3 ± 0.9 56 ± 10

(*continued*)

Table 28.2 (*Continued*)

Study	n (Type 1 diabetes)	Mean age (years)	Design	Duration	Type of exercise	VO_{2max}	HbA_{1c} before (%, mmol/mol)	HbA_{1c} after (%, mmol/mol)
HbA_{1c} deterioration								
Woo et al. [71]	10	11.21 ± 0.97	Control trial	12 wk, 3 times/wk	Aerobic exercise: treadmill	→	8.09 ± 0.5 65 ± 5	8.33 ± 0.8 65 ± 8
HbA_{1c} improvement								
Marrero et al. [72]	10	12–14	Case series	12 wk, 45 min, 3 times/wk	Aerobic fitness programme	↗	11.41 ± 4.47 101 ± 45	10.01 ± 3.21 86 ± 33
Bak et al. [73]	7	27.9 ± 7.1	Control trial	6 wk	Physical training	↗	7.9 ± 1.4 63 ± 15	7.7 ± 1.5 61 ± 16
Mosher et al. [22]	10	17.2 ± 2.9	Control trial	12 wk, 45 min, 3 times/wk	Aerobic exercise: circuit training	↗ 4%	7.72 ± 1.26 61 ± 14	6.76 ± 1.07 50 ± 11
Zoppini et al. [74]	53	NA	Cross-sectional study	Measurement of physical activity	30 regular exercise, 23 sedentary exercise	NA	7 ± 1 in regular exerciser group 53 ± 11	7.8 ± 1.2 in sedentary group 62 ± 13
Salvatoni et al. [75]	69	8.98 ± 3.9	Cross-sectional study	Measurement of physical activity for 1 wk	3 ± 2.9 h/wk	NA	6.3 ± 0.3 in group ≥7 h exercise/wk 45 ± 3	7.7 in group 2–4 h exercise/wk 61
Sideraviciute et al. [76]	19	14–19	Control trial	14 wk, 45 min, 2 times/wk	Aerobic exercise: swimming	↗	8.5 ± 0.4 69 ± 4	7.8 ± 0.3 62 ± 3
Herbst et al. [77]	19143	12.9–14	Cross-sectional study	0, or 1–2, or ≥3 times/wk	Measurement of regular physical activity	NA	8.4 ± 1.9 in 0 time/wk group 68 ± 20	8.0 ± 1.6 in 1–2 and ≥3 times/wk group 64 ± 17
Herbst et al. [78]	23251	12.7 ± 4.3 to 13.9 ± 3.1	Cross-sectional study	0, or 1–2, or ≥3 times/wk	Measurement of regular physical activity	NA	8.1 ± 1.9 in 0 time/wk group 65 ± 20	7.8 ± 1.6 in 1–2 and ≥3 times/wk group 62 ± 17
Ruzic et al. [79]	20	12.81 ± 2.14	Case series	2 wk intense exercise programme, 5 days of at least 1 h of exercise	Aerobic exercise: swimming, cycling, running	NA	8.28 ± 1.3 67 ± 14	7.92 ± 1.42 (but increase 2 mo after camp) 64 ± 15

All studies quoted have included people with type 1 diabetes in the intervention group, but the control group has either not been present or has included people without diabetes. The studies are listed in chronological order according to physical activity effect on HbA_{1c}.
BMI, body mass index; NA, not available.
Source: Adapted with permission from Chimen et al. 2011 [19].

significantly lowered HbA_{1c} (−0.71%; 8 mmol/mol). It also suggested that people needed to exercise more than three times a week and for longer than 12 weeks to see an effect on HbA_{1c}.

Studies in people with type 1 diabetes that have examined the effect of exercise on plasma glucose have not shown a consistent benefit on fasting glucose [28, 33, 69, 70]. However, these studies have shown, as seen with healthy individuals [50], that blood glucose decreases (without hypoglycaemia) around the time of exercise [37, 71]. The lack of glycaemic benefit as assessed by HbA_{1c} may result from rebound hyperglycaemia immediately following exercise, and better management of this may be beneficial.

Two main factors may account for the poor effect of exercise on HbA_{1c}. Many individuals with type 1 diabetes consume energy when physical active, either as a fuel source or to manage hypoglycaemia, and this may counteract any glucose-lowering effect of physical activity [50]. Similarly, people with type 1 diabetes who exercise regularly reduce their daily insulin dosages by 6–15% [28, 29, 48]. While this may be required to manage hypoglycaemia, these reductions may mask improvements in HbA_{1c}.

Vascular risk factors other than glucose

People with type 1 diabetes commonly have hypertension and dyslipidaemia that are associated with increased risk of vascular disease [85]. Most studies suggest that physical activity in people with type 1 diabetes improves lipid profile [22, 28, 30, 31, 33, 59]. These studies were of short duration (generally ≤4 months) and showed similar benefits to those seen in individuals without diabetes. High-density lipoprotein (HDL) cholesterol increased by 8–30%, while low-density lipoprotein (LDL) cholesterol and triglycerides decreased by 8–14% and 13–15%, respectively. Exercise also reduces apolipoprotein B, which is pro-atherogenic and is associated with premature mortality in type 1 diabetes [86], and increases the anti-atherogenic apolipoprotein A-I [28]. These benefits are independent of changes in glycaemia and weight and most pronounced in those with an adverse lipid profile.

Only four studies have examined the effect of physical activity on blood pressure in type 1 diabetes. All four studied young adults and used similar supervised exercise programmes. Two showed no benefits in systolic or diastolic blood pressure [31, 33] and two showed a 2–3% reduction in blood pressure [51, 59]. Three studies were small: 26, 14, and 20 participants, respectively [31, 33, 59]. The remaining study was larger and included 196 participants and was one of the studies to show a benefit [51].

People with type 1 diabetes have clear evidence of endothelial dysfunction and this is worse if microalbuminuria is present [21]. Regular exercise can reverse endothelial dysfunction [87] and improve vascular function, but this improvement is not as great as that seen in individuals without diabetes [31, 88]. Improved vascular function is also seen in vascular beds not supplying exercising muscles, suggesting that this is a global rather than local benefit of exercise. Benefits only persist while people are exercising regularly and cease soon after regular activity is stopped.

Although less insulin resistant than those with type 2 diabetes, people with type 1 diabetes are more insulin resistant than matched individuals without diabetes [21, 30]. This insulin resistance can be improved by up to 23% by both resistance and endurance exercises [29–31, 66].

The beneficial effects of physical activity on insulin resistance, as well as on lipid levels and endothelial function, suggest that physical activity should reduce vascular complications in type 1 diabetes.

Microvascular complications

Increased physical activity is associated with fewer diabetes-related complications in individuals with type 1 diabetes [89]. In the Pittsburgh IDDM Morbidity and Mortality study [90], in men but not women activity levels were inversely associated with the risk of nephropathy and neuropathy, but not retinopathy. However, a retrospective analysis of baseline physical activity in the Diabetes Control and Complication (DCCT) trial found that rates of development or progression of diabetic retinopathy, nephropathy, and neuropathy were unaltered by physical activity after a mean follow-up of 6.5 years [91].

Other studies have shown an inverse association between physical activity and the severity of several complications in type 1 diabetes [89, 92]. A follow-up study involving 1945 individuals with type 1 diabetes reported that those involved in either little leisure-time physical activity or low-intensity activity were more likely to have impaired renal function and more proteinuria as well as greater rates of retinopathy and cardiovascular disease when compared to their more frequently and more vigorously active counterparts [89]. Balducci et al. randomized 78 people (21 with type 1 diabetes and 57 with type 2 diabetes) without signs and symptoms of peripheral diabetic neuropathy to either supervised exercise or a control group [92]. The percentage of people with diabetes who developed motor and sensory neuropathy during the four-year study was significantly higher in the control than the exercise group, 17.0% vs 0.0% and 29.8% vs 6.4%, respectively. Thus, long-term aerobic exercise training seems to prevent the onset or modify the natural history of diabetes neuropathy [92].

More recently, a cross-sectional multicentre study of 18 028 people with type 1 diabetes reported that frequencies of retinopathy and microalbuminuria were lower in active compared with inactive people [93]. However, due to the cross-sectional design, no causality can be inferred. It remains unclear whether the presence of comorbidities affected people's ability to exercise or whether being physically active decreased the risk of developing these complications.

β-cell function

Type 1 diabetes is a chronic inflammatory autoimmune disease characterized by destruction of insulin-producing β cells and subsequent insulin deficiency [94]. This loss of β cells is gradual and at the time of diagnosis of type 1 diabetes significant β-cell function remains [95]. While it is generally assumed that the remaining β cells are completely destroyed soon after diagnosis, studies now indicate that these cells can persist for many years [96].

The preservation of these remaining β cells has important clinical benefits. A meal-stimulated C-peptide value of >200 pmol/l is associated with improved glucose levels for the first four years after diagnosis, a reduced risk of developing retinopathy and nephropathy, and a >50% reduction in hypoglycaemia rates [97]. Thus, interventions that have the potential to preserve β-cell function are worth striving for.

In diabetes animal models [13], healthy individuals [14], and people with type 2 diabetes, physical activity preserves β-cell function [15]. In a two-year prospective study of 125 children diagnosed with type 1 diabetes, those who were physically active had higher rates of partial remission compared to the inactive group [98]. Similarly, in a case-controlled study of adults recently diagnosed with type 1 diabetes, the honeymoon period was more than five times longer in men undertaking high levels of physical exercise, compared with age-, sex-, and body mass index (BMI)–matched sedentary controls [99]. In a pilot RCT of adults with newly diagnosed type 1 diabetes, β-cell

function, corrected for improved insulin sensitivity, was preserved by exercise [43]. A large RCT is needed to confirm these finding.

Bone density
People with type 1 diabetes have reduced bone mineral density and osteoporosis and increased risk of fracture [100]. A systematic review identified two RCTs and twelve observational (ten cross-sectional and two longitudinal) studies that had reported associations between physical activity and skeletal outcomes [101]. The two RCTs reported a beneficial effect of physical activity interventions on bone accrual in children. Results of the observational studies were mixed, with four finding a positive association with a measure of activity and a skeletal outcome and eight finding no effect. No studies have examined whether physical activity reduces fracture risk in people with type 1 diabetes.

Cancer
Whether people with type 1 diabetes are at increased risk of cancer is unknown [102]. Physical activity appears to protect the general population from cancer and improve outcomes in those who develop cancer (surgical outcome, side effects of chemotherapy, subsequent prevention of recurrence). Again, this has not been examined in type 1 diabetes.

Well-being
People with type 1 diabetes are two to three times more likely to have depression than the general population [85]. In young adults, physical activity is associated with significantly greater satisfaction with life and well-being [74], but these associations were not found in the one study that examined this in children [81].

Type 2 diabetes and exercise

Prevention of type 2 diabetes

Prospective observational studies
The earliest evidence that indicated that exercise might play a role in prevention of diabetes came from large prospective cohort studies. In these studies, higher levels of physical activity and/or cardiorespiratory fitness were consistently associated with reduced risk of developing type 2 diabetes [103–115]. After adjustment for confounding variables, the most active participants had a 25–60% lower risk of subsequent diabetes compared to those who were most sedentary. This reduction was seen regardless of the presence or absence of additional diabetes risk factors such as hypertension, parental history of diabetes, and obesity. In addition, similar magnitudes of risk reduction were seen with walking compared to more vigorous activity, when total energy expenditures were similar [111].

Non-randomized studies
The first large study to assess the effectiveness of lifestyle modification in preventing and treating diabetes was the Malmo study [116]. In this non-randomized study, 41 participants with type 2 diabetes and 181 with impaired glucose tolerance accepted enrolment into a 6–12-month intervention in which they were given advice to reduce energy intake and increase physical activity. The control group comprised 114 healthy individuals and 79 with impaired glucose tolerance who declined the intervention. At six-year follow-up, 10.6% of those with impaired glucose tolerance in the intervention group had progressed to type 2 diabetes, compared with 28.6% in the control group, a risk reduction of 63% [16]. Over 12 years, mortality among the controls was 14.0 per 1000 person-years, but only 6.5 per 1000 person-years in the intervention group [117]. This seminal study led on to several RCTs that have assessed the effect of lifestyle programmes in preventing type 2 diabetes.

Randomized studies
Table 28.3 summarizes the RCTs that have assessed whether lifestyle can prevent type 2 diabetes.

The China Da Qing Diabetes Prevention Outcome Study included 577 participants with impaired glucose tolerance who were randomized by centre into four arms – diet only, exercise only, diet and exercise, or control – and followed for six years [118]. The cumulative incidence of type 2 diabetes was 68% in controls, but only 44%, 41%, and 46% in the diet, exercise, and diet and exercise groups, respectively. The long-term follow-up is even more encouraging and indicates that the benefits from these lifestyle interventions continue for many years after completing *active treatment*; the so-called *legacy effect*. After 20 years' follow-up, 14 years after leaving the study, those in the interventional groups had 43% lower incidence and spent on average 3.6 fewer years with diabetes compared to the control group [119].

In the Finnish Diabetes Prevention Study, 522 people with impaired glucose tolerance were randomized to an exercise and diet intervention or control [120]. The intervention was intense and included individualized exercise plans, thrice-weekly supervised facility-based aerobic and resistance exercise, and seven one-hour meetings with a dietitian focusing on weight reduction, reduced fat intake, and reduced total caloric intake. Participants in the control group had one meeting per year. At four years, 22% of the control group and only 10% of the intervention group had developed diabetes, a 58% risk reduction. Again, a legacy effect was seen, with participants in the intervention arm having a 43% lower risk of developing diabetes three years after leaving the study [121].

In the American Diabetes Prevention Program [122], 3234 men and women with impaired glucose tolerance were randomly assigned to placebo, metformin, or a lifestyle-modification programme. Again, the lifestyle intervention was intense, with the participants provided with 16 lessons in the first 24 weeks. These lessons were delivered individually and covered diet, exercise, and behaviour modification. A minimum of two supervised exercise sessions per week and at least monthly contact with the study personnel were maintained thereafter. Cumulative incidences of type 2 diabetes were 11.0/100 person-years in the placebo group, 7.8 per 100 person-years in the metformin group, and only 4.8 per 100 person-years in the intensive lifestyle group. The risk of type 2 diabetes was 58% lower in the lifestyle group than in the placebo group, and 39% lower than in the metformin group [123].

The India Diabetes study randomized 421 men and 110 women with impaired glucose tolerance (mean age 45.9 ± 5.7 years, BMI 25.8 ± 3.5 kg/m^2) into four groups [125]. Group 1 was the control, Group 2 was given advice on lifestyle modification, Group 3 was treated with metformin, and Group 4 was given lifestyle modification plus metformin. The lifestyle advice was less intense than that given in the American and Finnish prevention studies. Participants in the lifestyle-modification group were asked to increase their activity to 30 minutes per day; if they were already achieving this goal, they were asked to maintain this level of activity. Exercise was not supervised. Diet modification was advised for each participant

Table 28.3 Controlled studies that have examined the prevention of type 2 diabetes.

Name	Number of participants	Design of study	Study participants	Detail of intervention	Duration	Outcome
Malmo Study [116, 117]	222	Non-RCT	C: 114 healthy and 79 individuals with IGT; LSM: 41 individuals with type 2 diabetes and 181 individuals with IGT	Individuals were given advice to reduce energy intake and increase physical activity. Intervention lasted for 0.5–1 yr	6 yr	Progression to type 2 diabetes: 10.6% vs 28.6% for LSM vs C group. A 63% risk reduction for the development of type 2 diabetes. Over 12 years, mortality was 14 vs. 6.5 per 1000 person-years in the C and LSM groups, respectively
China Da Qing Diabetes Prevention Outcome Study [118, 119]	577	RCT	Individuals with IGT randomized into four arms, D, E, D + E, or C	D: received prescribed diet, advice on healthy eating and caloric reduction; E: taught exercise with increased exercise intensity; D + E: include both diet and exercise instructions as D and E groups. All intervention groups received regular counselling sessions	6 yr, and follow-up at 20 yr	Cumulative incidence of type 2 diabetes was 44%, 41%, 46%, 68% in D, E, D + E, C groups, respectively. Legacy effect: D, E, and D + E groups had 43% lower incidence and spent average 3.6 fewer yr with type 2 diabetes compared to C group
Finish Diabetes Prevention Study [120, 121]	522	RCT	Individuals with IGT randomized into two arms: LSM and C	LSM: individualized exercise plans, thrice-weekly supervised facility-based aerobic and resistance exercise, and seven 1 h meetings with a dietitian focusing on weight reduction, reduced fat intake, and reduced total caloric intake	4 yr and follow-up at 7 yr	Development of type 2 diabetes 10% in LSM compared to C group. Risk reduction 58%. Legacy effect: 43% lower risk in intervention arm
American Diabetes Prevention Program [122, 123]	3234	RCT	Individuals with IGT randomized into three arms: placebo, MET, or an LSM programme	LSM included intense 16 lessons in first 24 wk, delivered 1 to 1 and covering diet, exercise, and behaviour modification. A minimum of two supervised exercise sessions per week and at least monthly contact with the study personnel were maintained thereafter	Average 2.8 yr	Cumulative incidences of type 2 diabetes were 11, 7.8, and 4.8 per 100 person-years in the placebo, metformin, and lifestyle groups respectively
Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males [124]	458	RCT	Men with IGT randomized into two arms in ratio 4:1: control (356) and LSM (102)	Control: if BMI $\geq$24 kg/m^2 advised to have 5–10% smaller meals, increase physical activity, and lose weight. If BMI$\leq$24 kg/m^2 told to avoid gaining weight. Seen every 6 months. LSM: BMI $\geq$22 kg/m^2 advised how to lose weight and increase weight. If BMI <22 kg/m^2 advice how to maintain weight by diet and exercise. Seen every 4 mo	4 yr	Cumulative 4 yr incidence of diabetes 9.3% in control group, versus 3.0% in LSM group, and reduction in risk of diabetes 67.4% ($p < 0.001$)

(*continued*)

Table 28.3 (*Continued*)

Name	Number of participants	Design of study	Study participants	Detail of intervention	Duration	Outcome
Indian Diabetes study [125]	531	RCT	Individuals with IGT randomized into four arms: C, LSM, MET, and LSM plus MET	LSM: asked to increase or maintain their activity to 30 min per day. Non-supervised exercise. Diet modification included reduction in total calories, refined carbohydrates, and fats, avoidance of sugar, and inclusion of fibre-rich foods. Individuals with LSM were contacted monthly by telephone and seen 6-monthly during the study	2.5 yr	3 yr cumulative incidences of diabetes were 55.0%, 39.3%, 40.5%, and 39.5% in control, LSM, MET, and LSM + MET, respectively. Relative risk reduction 28.5% with LSM, 26.4% with MET, and 28.2% with LSM + MET compared with control group
European Diabetes Prevention RCT [126]	102	RCT	Individuals with IGT over age of 40 and BMI 25 kg/m^2 randomized into two arms, LSM and C	C: standard diet and exercise advice. LSM: individual motivational interviewing aimed at weight reduction, increase in physical activity, fibre and carbohydrate intake, and reduction of fat intake	Mean follow-up of 3.1 yr	Absolute incidence of type 2 diabetes 32.7 per 1000 person-years LSE and 67.1 C. Incidence of diabetes reduced by 55% in LSM compared with C
Two-year-supervised resistance training prevented diabetes incidence in people with prediabetes [127]	137	RCT	Individuals with IGT randomized into four arms: C, AT, RT, or AT + RT	Control: continue activity as normal. AT: 60 min 3 times/wk. RT: 60 min all major muscles 3 times/wk. Combined: 30 min AT + 30 min RT 3 times/wk	2 yr	Incidences of diabetes adjusted by sex and age significantly decreased by 74% (combined), 65% (AT), and 72% (RT) compared with control group

AT, aerobic training; BMI, body mass index; C, control; D, diet; E, exercise; IGT, impaired glucose tolerance; LSM, lifestyle modification; MET, metformin; RCT, randomized controlled trial; RT, resistance training.

and included reduction in total calories, refined carbohydrates, and fats; avoidance of sugar; and inclusion of fibre-rich foods. To support the lifestyle modification, people were contacted monthly by telephone and seen six-monthly during the study. The median follow-up period was 30 months, and the three-year cumulative incidences of diabetes were 55.0%, 39.3%, 40.5%, and 39.5% in Groups 1–4, respectively. The relative risk reduction was 28.5% with lifestyle modification, 26.4% with metformin, and 28.2% with combine lifestyle modification and metformin compared with the control group.

In these prevention studies, weight loss seems to be the main factor in reducing diabetes incidence. In the US Diabetes Prevention Program, among those in the intervention arm for every kilogram in weight loss a 16% reduction in diabetes was seen, when adjustment for changes in diet and lifestyle were made [128]. Results from a meta-analysis also suggest that the effectiveness of these lifestyles programmes may be greater in those who are more overweight.

Weight loss, however, does not explain all the intervention effects. In the Indian Diabetes Prevention Programme, a 28.5% reduction in diabetes incidence was achieved without weight loss or reduction in waist circumference [125]. In the exercise intervention arm of the Da Qing study, a 46% reduction in diabetes incidence was achieved without weight loss [118]. These factors suggest that some aspects of diet as well as physical activity, not necessarily related to weight loss, may be involved in mediating the beneficial effect of lifestyle modification in the prevention of type 2 diabetes.

A recent study has examined the effect of exercise alone on preventing type 2 diabetes in people with impaired glucose tolerance [127]. In this study 137 people with impaired glucose tolerance were randomized into four groups. Group 1 was the control and continued normal activity, Group 2 did 60 minutes of aerobic exercise (dance) three times per week, Group 3 did 60 minutes of resistance training three times a week, and Group 4 did combined aerobic and resistance training for 60 minutes three times per week. After 24 months the incidence of diabetes was 69%, 22%, 26%, and 22% in Groups 1–4, respectively. The relative risk reduction was 72% with aerobic exercise, 65% with resistance training, and 74% with combined exercise compared with the control group.

Treatment of type 2 diabetes

There is very clear evidence that exercise alone has profound benefits in people with established type 2 diabetes. Figure 28.2 summarizes the benefits that people with type 2 diabetes can expect to see with exercise.

Physical fitness, cardiovascular disease, and mortality

People with type 2 diabetes have a significantly lower VO_{2max} than healthy age-, BMI-, and activity-matched participants without diabetes [129]. Meta-analysis of nine RCTs involving 266 people with type 2 diabetes, comparing exercise and control, shows that regular exercise, at least 50% of VO_{2Max}, improved overall VO_{2Max} by 11.8% in the exercise group versus a reduction of 1% in the control group. Additionally, higher-intensity exercise produces even larger improvements in cardiorespiratory fitness [130].

Observational studies have shown that increased physical activity improves cardiorespiratory fitness and lowers mortality rate in participants without diabetes [131, 132], while prospective studies in people with diabetes report that even walking for two hours a week is associated with less cardiovascular mortality; however, the effect is greater with three to four hours of walking a week [133]. No RCT has assessed the effect of improved physical fitness on mortality in type 2 diabetes.

Glycaemic management

Supervised exercise training

Structured exercise training is normally defined as an intervention in which people engage in a planned, individualized, and supervised exercise programme. The most recent meta-analysis that examined the effect of structured exercise training on HbA_{1c} in type 2 diabetes reported in 2011 [134] (Figure 28.3). This included 23 RCTs with 1533 participants. Studies had to be RCTs of ≥12 weeks' duration and had a control group of people with type 2 diabetes. Overall, structured exercise reduced HbA_{1c} by 0.7% (7 mmol/mol) compared to control participants. When dividing the studies into exercise type, 18 studies with 848 people demonstrated that structured aerobic exercise training reduced HbA_{1c} by 0.7% (7 mmol/mol), 4 studies with 261 people showed that structured resistance exercise training reduced HbA_{1c} by 0.6% (6 mmol/mol), and 7 studies with 404 people demonstrated

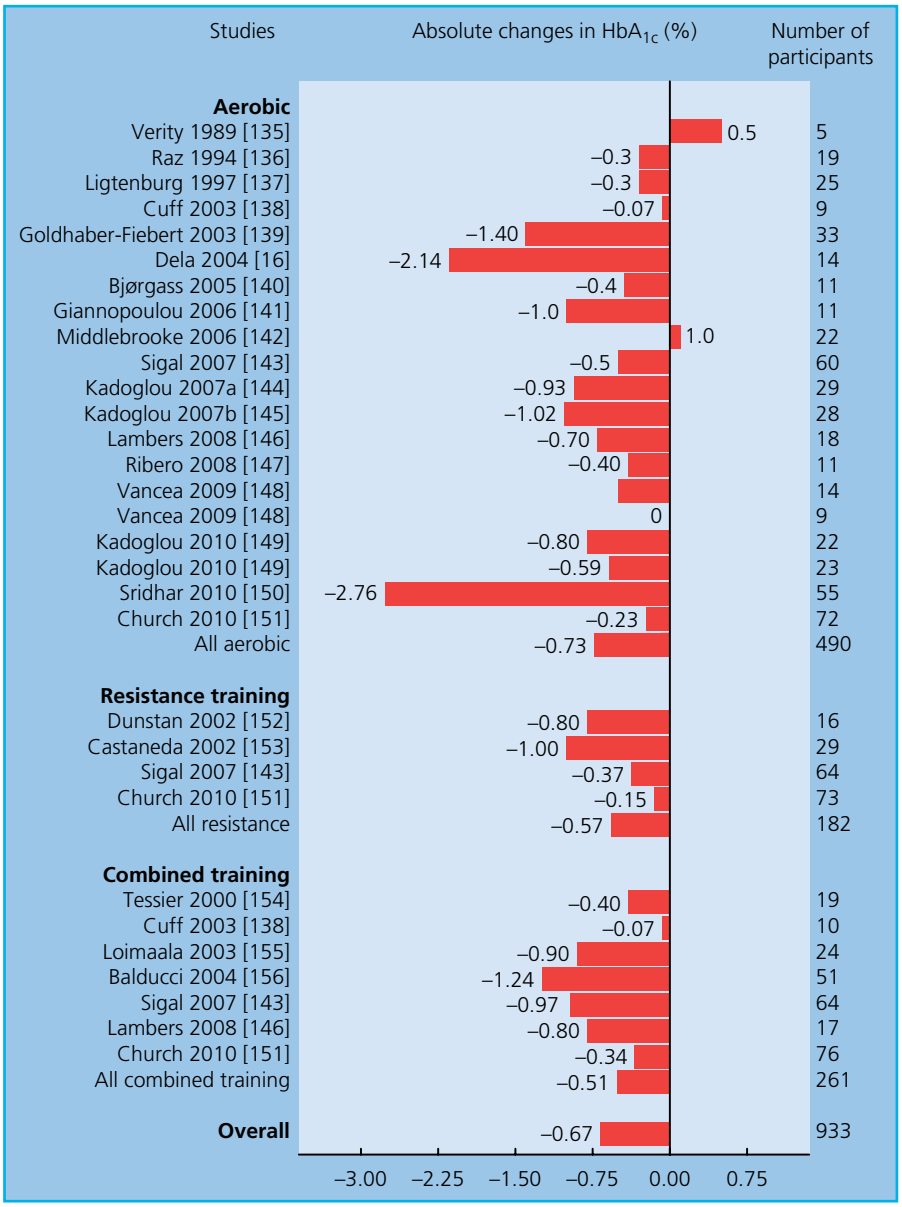

Figure 28.3 Absolute changes in glycated haemoglobin (HbA_{1c}) of individual studies of structured exercise training versus no intervention. Number of participants in each exercise regimen is shown in the box in white. Source: Adapted from Umpierre et al. 2011 [134].

that the combined aerobic and resistance exercise reduced HbA_{1c} by 0.5% (5 mmol/mol). This meta-analysis also showed that structured exercise duration of ≥150 minutes per week was associated with greater benefit than structured exercise duration of ≤150 minutes (0.9% vs 0.4%; 9 mmol/mol vs 4 mmol/mol reduction, respectively).

Using a meta-regression analysis, Umpierre et al. assessed the association between intensity and volume of supervised exercise training (aerobic, resistance, or combined) and HbA_{1c} changes in type 2 diabetes [157]. Higher baseline HbA_{1c} was associated with greater HbA_{1c} reduction with training. For supervised aerobic training and combined aerobic/resistance training, higher volume of exercise was associated with greater HbA_{1c} reduction. For example, each set of aerobic exercise added within the exercise week produced a 0.4% (4 mmol/mol) HbA_{1c} reduction. No exercise variables were found to be possible candidates to explain the effects of supervised resistance training.

A meta-analysis of RCTs that compared supervised resistant exercise with aerobic exercise in people with type 2 diabetes sought to clarify whether there was an optimum type of exercise for treating type 2 diabetes [158, 159]. The 12 included studies of 626 participants were RCTs of ≥8 weeks' duration that compared supervised resistant exercise with supervised aerobic exercise. Although there was a greater reduction of HbA_{1c} with supervised aerobic exercise compared to supervised resistant exercise, the difference was only 0.2% (2 mmol/mol) and not clinically significant.

Two RCTs have compared the three commonly used types of supervised exercise for treating type 2 diabetes, namely aerobic, resistance training, or a combination [143, 151] (Figure 28.4). In the Diabetes Aerobic and Resistance Exercise (DARE) trial [143], 251 previously sedentary individuals with type 2 diabetes were randomized into four arms: aerobic exercise training, resistance exercise training, combined aerobic and resistance exercise training, or a non-exercising control group. Compared to the control group, HbA_{1c} decreased significantly in the aerobic group by 0.5% (5 mmol/mol) and the resistance group by 0.4% (4 mmol/mol). In the combined exercise group, HbA_{1c} fell by an additional 0.5% (5 mmol/mol) compared with the aerobic group and 0.6% (6 mmol/mol) compared with the resistance group. In people with HbA_{1c} ≤7.5% (48 mmol/mol), HbA_{1c} only decreased significantly in the combined exercise training group.

Church et al. [151] randomized 262 sedentary people with type 2 diabetes to four groups: aerobic exercise training, resistance exercise training, combined aerobic and resistance exercise training, or a non-exercising control group. Compared with the control group, neither the resistance nor aerobic training produced a significant change in HbA_{1c}. For the combination training exercise group, a fall in HbA_{1c} of 0.3% (3 mmol/mol) was seen compared to the control group.

High-intensity interval training (HIIT) is the newest form of exercise to be tried in the management of type 2 diabetes, as it takes less time to perform and can produce similar physiological effects to longer duration of standard exercises. Recently a meta-analysis of ten small studies that aimed to quantify the effects of HIIT on markers of glucose regulation with control conditions or continuous training has reported [158]. Compared with control conditions, in people with type 2 diabetes HIIT did not produce a significant reduction in HbA_{1c}, but was superior to continuous training with a 0.37% (4 mmol/mol) HbA_{1c} reduction.

Physical activity advice

Although structured exercise training may be available to some people with type 2 diabetes, physical activity advice may be more feasible. Physical activity advice is normally defined as formal instructions to exercise regularly with or without an individualized exercise prescription. The most recent meta-analysis that assessed the effect of physical advice on HbA_{1c} in people with type 2 diabetes reported in 2011 [134] (Figure 28.5). This included 24 studies with 7025 participants. Overall physical activity advice produces a 0.4% (4 mmol/mol) decrease in HbA_{1c} compared to control. When the studies were broken down to those that included dietary advice, it was seen that physical activity advice in combination with dietary advice (12 studies, 6313 people) was associated with a 0.6% HbA_{1c} reduction (6 mmol/mol) compared with control, but physical activity advice alone (14 studies, 712 people) was not associated with HbA_{1c} changes.

Structured exercise training versus physical activity advice

The Italian Diabetes and Exercise Study [184] compared structured exercise training to physical activity advice. In the study, 606 individuals with type 2 diabetes were randomized to a full year of either physical activity advice alone, or supervised facility-based combined aerobic and resistance exercise training twice weekly plus physical activity advice. HbA_{1c} fell to a greater extent in the

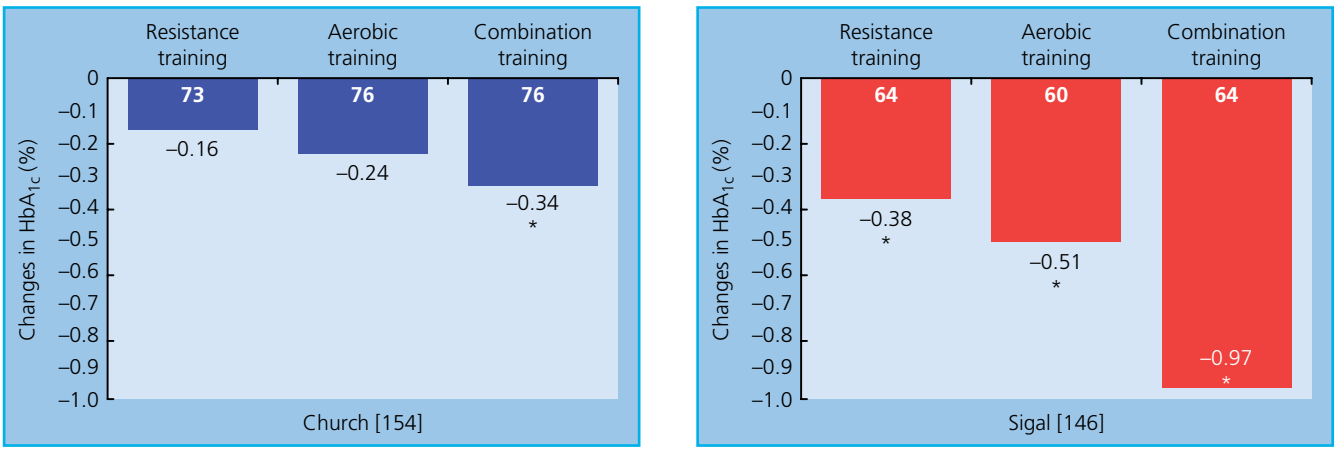

Figure 28.4 Reduction in glycated haemoglobin (HbA_{1c}) seen with different exercise regimens compared to control group in two studies, Church [150] and Sigal [143]. Number of participants in each exercise regimen is shown in the box in white. A star denotes significant improvement compared to control group.

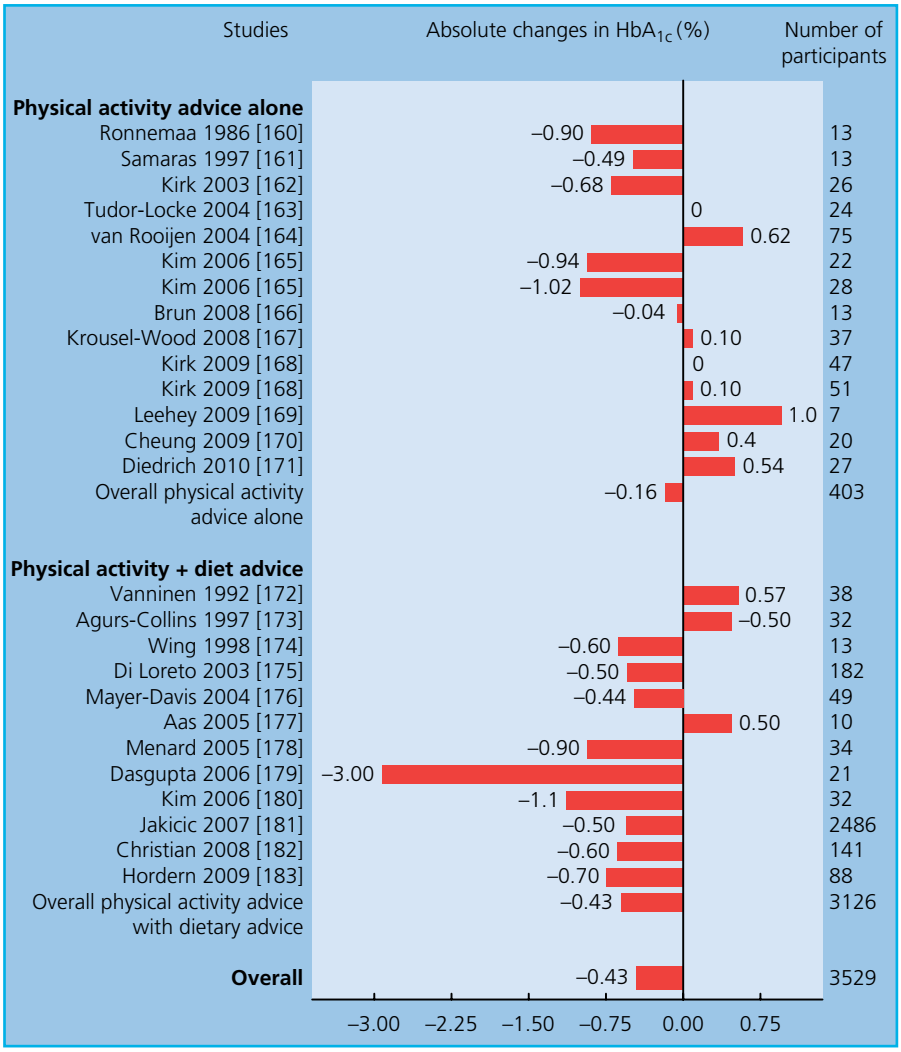

Figure 28.5 Absolute changes in glycated haemoglobin (HbA_{1c}) of individual studies of physical activity advice versus no intervention. Number of participants in each exercise regime is shown in the box in white.
Source: Adapted from Umpierre et al. 2011 [134].

supervised exercise group (0.4%; 4 mmol/mol) than the advice group (0.1%; 1 mmol/mol). This study suggests that supervised exercise programmes are more effective than physical activity advice.

Vascular risk factors other than glucose

In healthy people, aerobic and resistance training lower both systolic and diastolic blood pressure, whereas combined training only lowers diastolic blood pressure [185]. In 2014 Figueira et al. conducted a meta-analysis to assess the effect of physical activity advice alone or structured exercise training on blood pressure in type 2 diabetes [186]. They identified 30 RCTs (2217 participants) of structured exercise training and 21 RCTs (7323 participants) of physical activity advice alone. Overall, structured exercise reduced systolic blood pressure by 4 mmHg and diastolic blood pressure by 2 mmHg compared to controls. Greater reductions in blood pressure were seen when exercise duration was ≥150 minutes and when the intensity of the exercise was higher. When exercise training was broken down into exercise type, compared to control, aerobic exercise training reduced systolic blood pressure by 5 mmHg and diastolic blood pressure by 2 mmHg, and resistant exercise training reduced systolic blood pressure by 4 mmHg and diastolic blood pressure by 3 mmHg. Combined exercise training was not associated with a reduction in blood pressure. Physical activity advice alone produced a 3 mmHg reduction in systolic blood pressure and a 1 mmHg reduction in diastolic blood pressure.

Several studies have examined the effect of aerobic and combined aerobic and resistance supervised exercise on lipids in type 2 diabetes. In a meta-analysis, both reduced triglycerides by 0.3 mmol/l but had no effect on HDL cholesterol or LDL cholesterol [187]. Only one study has assessed the effect of resistance training and found no effect on total cholesterol, HDL cholesterol, LDL cholesterol, or triglycerides [176].

People with type 2 diabetes have impaired endothelial function [188, 189], which is a powerful and independent predictor of long-term cardiovascular events [190, 191]. Only a few small studies have assessed the effect of exercise on endothelium function in type 2 diabetes, but a meta-analysis of 5 studies including 217 participants reported that supervised exercise improved endothelium function [191].

Insulin resistance is one of the hallmarks of type 2 diabetes and is involved in the pathogenesis of hypertension and cardiovascular disease. Both aerobic and resistance training improve insulin resistance in type 2 diabetes [138]. Although in healthy individuals resistance exercise has a greater effect on insulin sensitivity than aerobic exercise, there is insufficient evidence to confirm whether this is the case in type 2 diabetes [192].

Microvascular complications

That fact that exercise improves HbA_{1c} and blood pressure, the two key risk factors in the development of diabetic microvascular complications, suggests that regular exercise should protect against microvascular complications. Few studies have examined whether this is the case. Impaired exercise capacity is associated with diabetic nephropathy and retinopathy [193]. In retrospective and prospective cohort studies, regular physical activity was associated with reduced progression and development of diabetic kidney disease [194, 195]. In the Look Ahead study, people randomized to the intervention arm (diet, exercise, and weight loss) were less likely to develop retinopathy or neuropathy [196]. In contrast, in the Japan Diabetes Complications Study in which 2033 participants were randomized to a lifestyle intervention (diet and exercise) or usual care, there was no difference in incident retinopathy or nephropathy between groups at eight years' follow-up [197]. No RCTs have examined the effect of exercise alone on microvascular risk in people with type 2 diabetes.

β-cell function

In the UK Prospective Diabetes Study, progressive decline of β-cell function was associated with worsening of glycaemic levels in people with type 2 diabetes, irrespective of treatment strategy [198]. Thus, maintenance of β-cell function is important to meet glucose targets in people with type 2 diabetes. Several studies have shown that aerobic exercise of varying intensity improves insulin secretion in type 2 diabetes [199–202].

Bone mineral density

People with type 2 diabetes are at increased risk of fractures despite normal, or even increased, bone mineral density [203]. This increase in fracture risk may be due to altered bone architecture or an increased risk of falling due to neuropathy. No studies has assessed the effect of physical activity on bone mineral density or fracture risk in type 2 diabetes.

Cancer

Type 2 diabetes is associated with an increased risk of developing cancer [203]. In the general population regular physical activity reduces cancer risk and improves outcomes in those who develop it. Again, no studies have examined whether this holds true for people with type 2 diabetes.

Well-being

People with type 2 diabetes have a higher chance of developing depression [204, 205]. They also have a poorer quality of life [206] and a higher prevalence of general anxiety disorder (14%) than the general population [207]. The effects of exercise training on quality of life, symptoms of depression and anxiety, and emotional well-being in type 2 diabetes were reviewed in 2014 [208], with two further studies since then [215, 225]. A summary of all studies is shown in Table 28.4. No form of exercise improved quality of life and emotional well-being, while depressive symptoms were only improved by resistant training and anxiety symptoms were only improved by aerobic training.

Table 28.4 Effect of exercise on well-being.

		Number of studies	Length of interventions (wk)	Number of participants	Results
Quality of life	Aerobic	5	8, 16, 16 and 52, 12 and 12	18, 50, 44, 29, 38	4 found no effect [146, 208–211] and 1 found effect on physical health and sleep subscales but not other subscales [212]
	Resistance	5	16, 16, 12 and 26, 16 and 12	58, 48, 110, 37, 30	3 found no difference [213–215], 1 found a significant effect [216], and 1 found effects on general health subscale [170] but no effect on other subscales
	Combined	11	24, 52, 16 and 52, 12 and 26, 8, 12, 26, 12, 16, 16	84, 606, 64, 109, 36, 77, 43, 28, 38, 29	6 found no effect [146, 154, 167, 210, 213, 217]. 4 found improvement across all measures of quality of life [218–221]. Remaining 1 found improvement in emotional role, mental health, and vitality, but not for other subscales [222]
Well-being	Aerobic	3	6, 8, 8	58, 40, 20	2 showed improvement [223, 224] and 1 no improvement [225]
	Resistance	2	8, 12 and 26	20, 110	One showed improvement [225], the other did not [213]
	Combined	1	12 and 26	109	No effect [213]
Depression	Aerobic	2	6 and 8	78, 58	Both showed no effect [223, 226]
	Resistance	1	16	58	Improved [216]
	Combined	1	8	36	No effect [222]
Anxiety	Aerobic	1	6	58	Reduced anxiety [223]
	Resistance	—			
	Combined	—			

Physical activity and gestational diabetes

Prevention of gestational diabetes

Gestational diabetes (GDM) is a condition in which women without a previous diagnosis of diabetes develop glucose intolerance during pregnancy (Chapter 71) [227]. The prevalence of GDM ranges from 1% to 14% depending on the diagnostic criteria used and the population being studied [228]. It is associated with adverse maternal and fetal outcomes; women with GDM have an increased risk of developing GDM in subsequent pregnancies and type 2 diabetes. Offspring of mothers with GDM are at high risk of macrosomia [229] and as adults are more likely to develop obesity [230] and type 2 diabetes [231]. Preventing GDM is therefore a clinical priority.

Several prospective studies have shown that low physical activity is associated with the development of GDM. In the largest of these studies, including 21 765 women, Zhang et al. found that when comparing the highest with the lowest quintiles of vigorous activity there was a relative risk reduction of 0.77 [232]. Among women who did not engage in vigorous activities, women who briskly walked ≥30 minutes or climbed ≥15 flights of stairs daily also had a lower risk of GDM [232].

Two recent systematic reviews have examined whether prenatal physical activity prevents GDM. Sanabria-Martinez et al. reviewed RCTs of sedentary healthy women or those with low levels of physical activity (exercising <20 minutes on <3 days per week) with uncomplicated and singleton pregnancies [233]. In their review, 13 RCTs with 2873 pregnant women met the inclusion criteria, of which only 3 reported ethnicity and involved white women. Exercise reduced the risk of GDM by 31%, with this increasing to 36% if started early in pregnancy. Davenport et al. identified 46 RCTs with 14 923 pregnant women and found that prenatal exercise was associated with 24% lower odds of developing GDM compared with no exercise [234]. Both reviews felt that larger, better-quality studies were needed to confirm or refute these findings.

Treatment of gestational diabetes

Regular exercise during pregnancy is associated with many benefits, including improved cardiorespiratory fitness, less low back pain, reduced urinary incontinence, reduced depressive symptoms [235], and less weight gain in pregnancy [236]. Although diet and exercise are recommended as the first step in managing GDM, there is debate about whether there is clear evidence about the effectiveness of exercise. A 2006 Cochrane review concluded that 'there is insufficient evidence to recommend, or advise against, diabetic pregnant women to enrol in exercise programs. Further trials, with larger sample size, involving women with gestational diabetes, and possibly type 1 and 2 diabetes, are needed to evaluate this intervention' [237]. A systematic review identified seven studies that examined the effect of exercise in managing GDM [238]. Five studies found improvements in glycaemic levels and/or a limitation in insulin use [239–243], but two reported no effect [244, 245].

Exercise advice for people with type 1 diabetes or type 2 diabetes

Exercise guidelines

The American Diabetes Association has published recommendations and guidelines for exercise in individuals with diabetes [246]. These and other guidelines are summarized in Table 28.5.

Table 28.5 Exercise guidelines for adults and children with type 1 diabetes and type 2 diabetes and pregnant women with diabetes.

Categories	Physical activity recommendations
Adults with type 1 diabetes and type 2 diabetes	At least 150 min/wk of moderate-intensity or 75 min/wk of vigorous-intensity aerobic physical activity, or equivalent combination of the two. This should be spread over 3 d with no more than 2 consecutive days without exercise Additionally, muscle-strengthening activities that involve all major muscle groups should be performed on 2 or more days of the week Reduction in sedentary time is also recommended [206] Flexibility training and balance training are recommended 2–3 times/wk for older adults with diabetes
Children and teens with type 1 diabetes and type 2 diabetes	At least 60 min of physical activity daily, which should include vigorous-intensity aerobic activity, muscle-strengthening activities, and bone-strengthening activities at least 3 d of the week [206]
Pregnancy in women with diabetes	At least 30 min or more of moderate exercise daily if there are no medical or obstetric complications [206]

Source: Adapted from Colberg et al. 2016 [246].

Where possible, advice should be tailored to the individual, taking into account their interests, level of fitness, possible contraindications, and personal goals. There are many examples of people with diabetes competing at the highest level, so diabetes should not interfere with an individual's sporting goal and treatment should be adjusted according to the demands of the activity. For activities and competitions considered to be high risk for individuals with diabetes (e.g. car racing, flying, diving), individual governing bodies should be consulted regarding restrictions in competition. It is also important to note that the use of insulin is prohibited by the World Anti-Doping Agency, and elite-level athletes with diabetes will require a Therapeutic Use Exemption (TUE) certificate prior to competition.

Most guidelines recommend ≥150 minutes of moderate aerobic activity, and/or ≥90 minutes of vigorous aerobic exercise every week, and that this activity be spread over at least three days [246]. A day's activity need not occur in a single session, but may be accumulated in bouts of ≥10 minutes at a time, performed throughout the day. Performing ≥150 minutes of moderate activity is associated with greater benefit, so if an individual has reached the target of 150 minutes they should be encouraged to do more if possible.

In addition to aerobic exercise, many guidelines also suggest that resistance training should be carried out at least twice per week, as combining aerobic exercise with resistance training has the greatest effect on HbA_{1c}. Ideally at least three sets of resistance exercise should be performed at each session, as the resistance exercise studies that have used ≥3 sets have shown the greatest reduction in HbA_{1c} [49, 152, 247]. Weight lifting is safe in people with cardiac disease [248] and is not associated with increased proliferative retinopathy risk [248].

The guidelines recommend that people with diabetes should also reduce their sedentary time [246]. This is because higher sedentary

time is associated with a poorer metabolic profile in type 2 diabetes and reduced sedentary time improves metabolic profile [249].

Minimizing risk of exercise-related adverse events

Assessment

There is often concern about the safety of exercise for people with diabetes, although for most people the benefits of exercise will outweigh the risks. Prior to starting exercise for the first time or when beginning a programme of vigorous physical activity, people with diabetes should be assessed for conditions that might increase risks associated with certain types of exercise or predispose them to injury. Table 28.6 provides guidance on what pre-exercise assessment should be undertaken.

Specific exercise considerations for people with type 1 diabetes

In healthy individuals without diabetes, changes in insulin and counter-regulatory hormone secretion during exercise are dependent on the type of exercise being performed [250]. These changes facilitate an increase in liver glucose production to match skeletal muscle glucose uptake [162]. A change in the secretion of these hormones is also seen post-exercise to facilitate recovery and adaptation to exercise. As a result, blood glucose levels remain relatively stable before, during, and after exercise.

In people with type 1 diabetes, because insulin lies in subcutaneous depots and is not under regulation, insulin levels do not change in a physiological manner during exercise, thus they cannot fall in response to exercise and there may be impaired secretion or action of counter-regulatory hormones. This impairs normal fuel regulation [251]. The inability of the pancreas to modulate insulin and counter-regulatory hormones (in particular glucagon) following exercise can also hamper recovery and adaptation to exercise. This increases the risk of hypoglycaemia both during and following exercise. Furthermore, hyperglycaemia prior to and following some types of exercise can be problematic [252]. Consequently, people with type 1 diabetes have three main problems when exercising:

- Problems controlling their blood glucose during and immediately following exercise.
- Unexplained severe hypoglycaemia, particularly at night.
- Reduced performance through excessive fatigue and reduced muscle strength.

To help overcome these problems, people need to understand how different exercises affect glucose, know when it is safe to exercise, and have strategies to manage glucose during and after exercise.

How different exercise affects blood glucose

Both intensity and exercise type will determine what happens to blood glucose concentrations (Figure 28.6). The most rapid drop in blood glucose occurs during aerobic or endurance exercise, when circulating insulin suppresses metabolic fuel production and increases muscle glucose uptake. With intermittent high-intensity exercise, there is a mixture of both aerobic and anaerobic exercise, which is characteristic of team sports and children's play; blood glucose is either stable or falls slowly [253]. High-intensity or anaerobic exercise tends to raise blood glucose, as a result of the increased catecholamines that are normally seen with these exercises [254].

When it is safe to exercise

Hypoglycaemia in the 24 hours preceding exercise blunts the counter-regulatory hormone response to exercise-induced hypoglycaemia, placing an individual at greater risk of exercise-induced

Table 28.6 Pre-exercise assessment and advice for people with diabetes complications.

Complication	Advice
Cardiovascular disease	Symptoms of cardiovascular disease should be asked about and where there is concern referral to a cardiologist for further assessment is indicated There is no evidence for screening of asymptomatic individuals Cardiovascular assessment is recommended for individuals with diabetic autonomic neuropathy
Peripheral neuropathy	It is vital to ensure that appropriate footwear is worn and feet are examined regularly, particularly if peripheral neuropathy is present Weight-bearing exercise should be avoided in those with active foot disease Walking does not increase the risk of ulceration in individuals with peripheral neuropathy Exercise delays the progress of neuropathy and so should be encouraged
Retinopathy	When proliferative or severe non-proliferative retinopathy is present, it may be sensible to avoid vigorous activity (both aerobic and resistance) because of the possible increased risk of vitreous haemorrhage or retinal detachment
Nephropathy	No evidence for restriction of any type of exercise in individuals with diabetic kidney disease Exercise can reduce progression and so should be encouraged

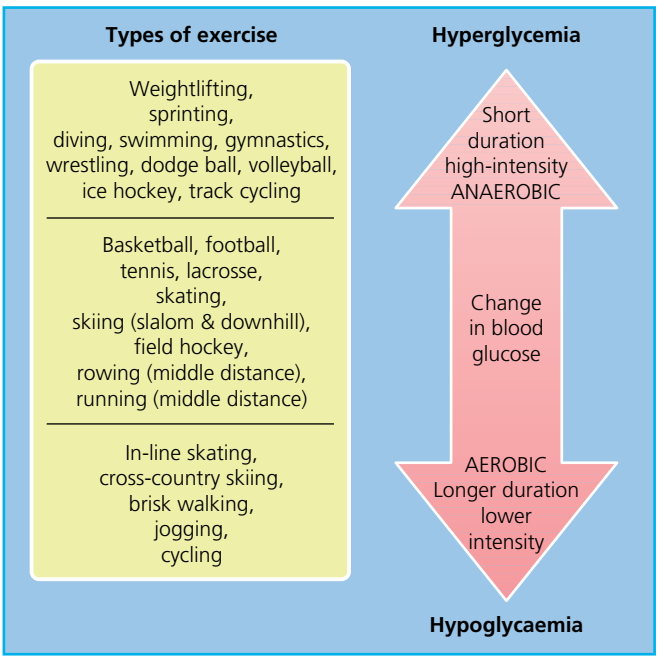

Figure 28.6 Effects of different sports on blood glucose concentrations.

Table 28.7 Insulin dose adjustment table for exercise.

		Intensity		
	Duration	**Low (<50 MHR % or Borg scale 10)**	**Medium (50–75% MHR or Borg scale 10–15)**	**High (>75% MHR or Borg scale>15)**
% Dose reduction	<30 min	10–20%	20–45%	40–60%
	30–60 min	20–30%	30–55%	50–75%
	>60 min	30–50%	45–70%	100%

MHR, maximum heart rate. Borg scale is based on the Borg rating of perceived exertion (see [265]).

hypoglycaemia. This risk is proportional to the severity of the preceding hypoglycaemia, with the effect starting at 3.9 mmol/l [255]. There is currently no evidence to guide individuals as to when it is safe to exercise following a hypoglycaemic episode. However, a consensus document suggests the following [256]:

- Not to exercise within 24 hours of severe hypoglycaemia requiring third-party assistance.
- Not to exercise within one hour of self-treated hypoglycaemia. If an individual insists on doing so, they should treat the hypoglycaemia and wait 45–60 minutes once the glucose is stable before commencing activity.
- Take extra precautions when there has been an episode of self-treated hypoglycaemia within the previous 24 hours. This would include more frequent glucose testing, exercising with an informed partner, and, if possible, including an anaerobic component to their training, because this will tend to raise their blood glucose.

If there is hypoglycaemia during exercise, exercise should be discontinued and the hypoglycaemia treated. The individual should wait at least 45 minutes before recommencing activity (or until blood glucose is stable). If an episode of severe hypoglycaemia occurs during exercise, then the activity should be stopped altogether because of the high risk of further hypoglycaemia.

When the blood glucose level is ≥15 mmol/l before exercise, the presence of ketones (capillary or urine) should be assessed [256]. If ketones are present, exercise is contraindicated and supplemental insulin should be considered (1 unit for 2–3 mmol/l glucose reduction). Exercise should only be commenced when ketone free and blood glucose is <15 mmol/l [257]. Where the blood glucose level is ≥15 mmol/l and ketones are not present, advice depends on timing of the last meal (and, therefore, last quick-acting insulin dose). If a meal has been eaten in the last 1–2 hours, exercise may be commenced with close blood glucose monitoring. If the last meal was eaten ≥2 hours ago, then 30% of the usual correction dose should be given.

Strategies to manage glucose during exercise

An initial strategy for managing blood glucose during exercise is to replace the carbohydrate that will be used during exercise orally. In its simplest form, this is a fixed carbohydrate replacement regimen. In adults, we initially recommend 15 g of carbohydrate for every 30 minutes of exercise [258]. Although activities vary widely in terms of fuel requirements, this range represents a safe starting point for most people beginning moderate-intensity exercise. Estimates of carbohydrate requirement based on body mass can be used in preference to fixed-dose carbohydrate replacement. For moderate and intensive activity, 0.5 g/kg/hr and 1 g/kg/hr, respectively, may be used [259].

An alternative approach that adjusts for the variable fuel requirements of different exercises is using standardized tables. These have been devised to help athletes of different body weight estimate carbohydrate requirements for different exercise intensities [260]. The maximum rate of enteral glucose absorption is 1 g/min. Therefore, carbohydrate requirement exceeding 60 g of glucose per hour would need to comprise a combination of glucose and fructose. In general, once carbohydrate requirements for exercise exceed 60 g/hr, we recommend altering insulin doses.

Several studies have examined insulin dose reductions for exercises of different intensities. This has enabled the development of dose reduction tables (Table 28.7). These tables tend to refer to changes to fast-acting insulin and therefore relate to exercise undertaken within two hours of eating (three hours if on soluble human insulin). To gain the most from these reductions, exercise is best conducted within 30 minutes after eating, and the meal or snack should predominantly contain low glycaemic index carbohydrate [261]. Reduction in basal insulin can, however, be helpful if people are undertaking prolonged exercise in the morning, or in the afternoon two hours after their meal.

Strategies to manage glucose post-exercise

Following exercise, carbohydrate is required to replenish muscle and liver glycogen stores. Protein is also needed for post-exercise muscle repair and synthesis. Failure to provide this increases the risk of hypoglycaemia in the subsequent hours, and fatigue in subsequent exercise sessions. Initially individuals should be advised to take snacks equivalent to 1 g/kg body weight of carbohydrate and 0.3 g/kg of protein [262]. This snack should be taken with insulin, as this increases carbohydrate storage in the exercising muscles and liver [263]. Initially we recommend a third of their normal insulin-to-carbohydrate ratio.

There is a risk of hypoglycaemia several hours after exercise through an increase in insulin sensitivity. If individuals have exercised during the morning or early afternoon, they should monitor their blood glucose and take extra carbohydrate as needed. If exercise has been undertaken in the late afternoon or evening, this may lead to nocturnal hypoglycaemia. To prevent this, people should reduce their evening basal insulin by 20% or take extra carbohydrates before going to bed.

High-intensity aerobic and anaerobic exercise can lead to post-exercise hyperglycaemia through increased hepatic glucose output

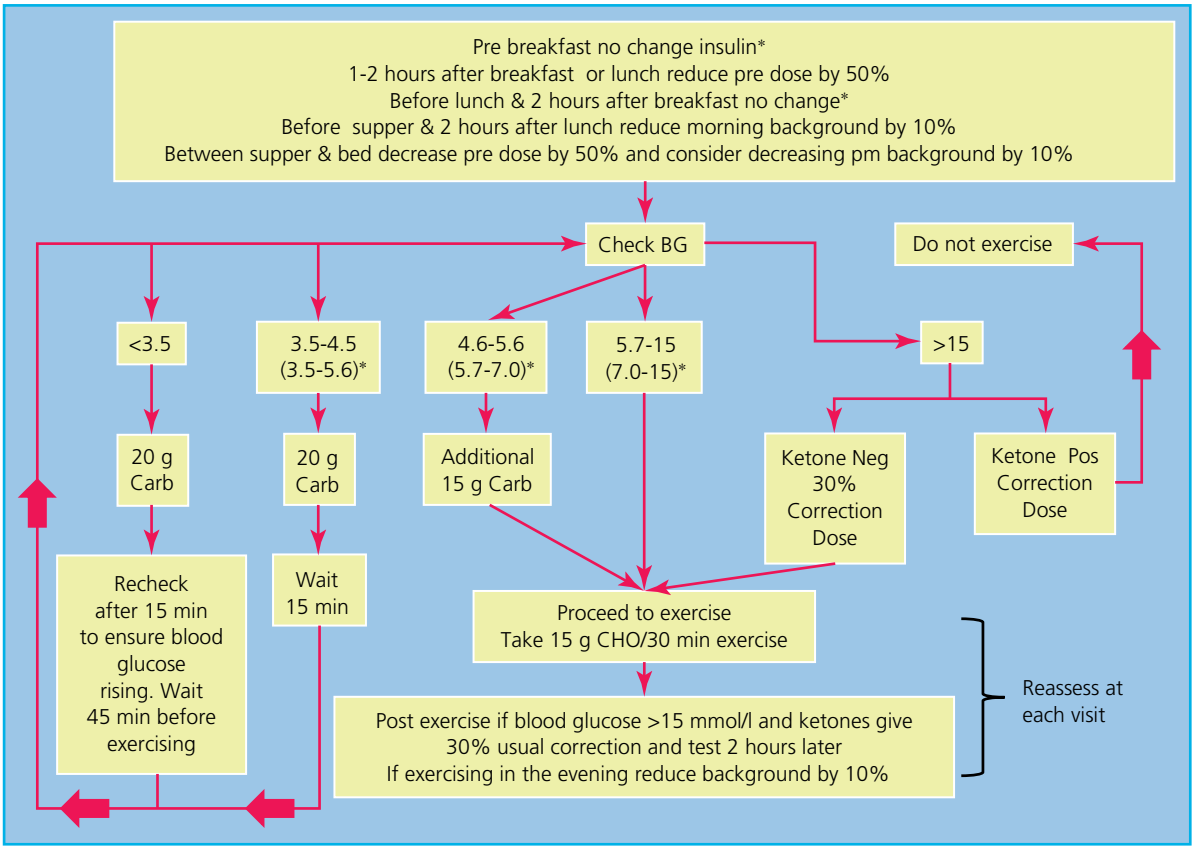

Figure 28.7 Algorithm for people with type 1 diabetes suggesting changes to insulin and carbohydrate (CHO) intake when exercising. Note that different blood glucose (BG) levels are used in this algorithm if exercising before breakfast or when exercising two hours after breakfast and before lunch, when no changes in insulin dosages are made – this is detonated by a star. Blood glucose values are given in mmol/l. To convert to mg/dl, these should be multiplied by 18.018.

and muscle insulin resistance, brought on by increased production of counter-regulatory hormones [264]. This means that additional insulin may be needed post-exercise. While there is currently no evidence to guide insulin correction dose, we recommend starting with 30% of the usual correction dose for blood glucoses ≥14 mmol/l post-exercise. Figure 28.7 shows a simple algorithm that brings together all this advice.

Specific considerations for people with type 2 diabetes

In people with type 2 diabetes, exercise does not typically cause hypoglycaemia and so carbohydrate supplementation is usually unnecessary. If blood glucose declines rapidly during exercise, as may occur in individuals taking oral anti-diabetes agents or insulin, the drug dosage should be reduced or withheld on exercising days.

Conclusion

Exercise improves well-being and reduces the risk of heart disease, cancer, and type 2 diabetes in the general population. In individuals with established type 1 diabetes or type 2 diabetes, regular exercise improves cardiovascular risk factors such as blood pressure and lipids and is associated with decreased mortality and decreased frequency and severity of diabetes-related complications. For individuals with type 2 diabetes, regular exercise improves metabolic management, as demonstrated by decreases in HbA_{1c}. This chapter has summarized the existing evidence about the effects of exercise in type 1 diabetes, type 2 diabetes, and gestational diabetes. A summary of current exercise recommendations is provided, along with practical advice on managing exercise training in individuals with both type 1 diabetes and type 2 diabetes.

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29 Monitoring Diabetes

Emma English
Faculty of Medicine and Health, University of East Anglia, Norfolk, UK
Department of Clinical Biochemistry, Norfolk and Norwich University Hospital Trust, Norwich, UK

Key points

- Glycated haemoglobin (HbA_{1c}) is now used for both the long-term monitoring of people with diabetes and the diagnosis of type 2 diabetes. HbA_{1c} and blood glucose remain the mainstay for monitoring glycaemic levels.
- HbA_{1c} values are reported in SI units (mmol/mol) and derived % units using a stable master equation. All methods for HbA_{1c} should now be standardized to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference measurement procedure.
- People with type 1 diabetes should have HbA_{1c} monitored every 2–6 months, depending on the level and stability of blood glucose and change in therapy.
- People with type 1 diabetes should be encouraged to self-monitor blood glucose with capillary blood glucose meters or continuous glucose monitoring systems. With treatment regimens intended to produce intensive glycaemic management, testing should be frequent (e.g. four or more times a day).
- For people with type 2 diabetes, glycaemic levels should be monitored using high-precision methods for measurement of HbA_{1c} every 3–6 months, depending on the level and stability of blood glucose and change in therapy.

Why monitor?

The field of diabetes care has advanced significantly over the past 50 years and people with diabetes can expect to achieve optimal glycaemic levels through multiple pharmacological and non-pharmacological approaches. Coupled with the advances in treatment of the disease, methods for detecting diabetes and its complications have also advanced. Without accurate and precise measures of blood glucose and glycated haemoglobin (HbA_{1c}) to monitor the efficacy of any intervention, tight glycaemic levels would not be achievable in a safe manner. Therefore, it is essential that people with diabetes have a clear regimen for monitoring their diabetes and are supported with education programmes to understand the role that testing plays in their care.

The aim of monitoring in diabetes includes:

- Allowing people with diabetes to understand the nature of their disorder.
- Determining the optimum times for initiating therapeutic intervention.
- Guiding the day-to-day adjustment of treatment.

Choosing the optimal target for monitoring and which assay is important ensures the best outcomes not only for an individual, but also at a population level, where small differences between the performance of tests, the frequencies with which they are carried out, and their costs may lead to important differences in outcomes and overall costs of care.

HbA_{1c} and blood glucose are the two most frequently used measures of glycaemia in current practice. HbA_{1c} provides information about overall glucose levels in the previous 6–8 weeks, allowing assessment of the need for therapy and therapeutic response with minimal within-person variation in measurement. Blood glucose measurements provide information about the day-to-day levels, variation in levels, and response to therapeutic intervention. This chapter will describe the tests for HbA_{1c} and glucose levels, the characteristics of these tests, the technology used in measuring their levels, and their clinical application in type 1 diabetes and type 2 diabetes. Additionally it will explore the role of other glycated proteins and the increasing role of point-of-care testing in diabetes monitoring. Newer and emerging technologies to assess glycaemia, including continuous glucose monitoring (CGM), are covered in Chapter 32.

Tests and their characteristics

Glycated haemoglobin

HbA_{1c} measurement plays a pivotal role in the management of people with diabetes and in the diagnosis of people with type 2 diabetes. HbA_{1c} levels are associated with the response to treatment and the risk of developing complications, and therefore provide an evidence-based marker with which to judge the impact of glucose-lowering treatment and prognosis. The outcomes of trials such as the UK Prospective Diabetes Study (UKPDS), the Diabetes Control and Complications Trial (DCCT), and Epidemiology of Diabetes Interventions and Complications (EDIC) clearly demonstrate the association between improved glycaemic levels and microvascular and, to a lesser extent, macrovascular complications of diabetes.

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Glycohaemoglobin, glycosylated haemoglobin, glycated haemoglobin, glucosylated haemoglobin, fast haemoglobins, HbA_1, HbA_{1a+b}, HbA_{1c}, and total glycohaemoglobin have all been used to refer to haemoglobin with the addition of glucose. However, with the introduction of standardization of HbA_{1c} testing, many of these terms are no longer in use and the term HbA_{1c} (sometimes abbreviated to A_{1c}) is the commonly accepted term.

HbA_{1c} is reported in SI units (from the French Système International d'Unités) of mmol/mol (mmol HbA_{1c}/mol Hb $A_0 + HbA_{1c}$). While this is the internationally recognized unit for HbA_{1c}, it is still common to see the former units of % (the proportion of glycated to total levels of haemoglobin) used in many texts [1]. There are numerous conversion tables available to convert between the two units.

HbA_{1c} is formed by the binding of glucose to the β chain of haemoglobin in circulating red blood cells. The reaction between circulating glucose and haemoglobin is spontaneous and non-enzymatic, therefore HbA_{1c} formation is dependent on glucose concentration and duration of exposure. HbA_{1c} is formed slowly and continuously throughout the ~120-day lifespan of the red cell; however, due to the continual turnover of red cells in circulation, the most recent 60 days account for up to 75% of the influence on HbA_{1c} concentration.

Glucose, in the open-chain format, binds to the N-terminal valine of the β chain of haemoglobin A_0 [2] to form an aldimine (Schiff base), before undergoing an Amadori rearrangement to form a more stable ketoamine [3,4] (Figure 29.1). This is a non-enzymatic process that occurs continuously *in vivo* [4]. Glycation of haemoglobin is atypical, because the reaction occurs predominantly between glucose and the N-terminal valine of the β chain of haemoglobin to form HbA_{1c} [5]. Although this is the favoured reaction *in vivo*, other aldoses (galactose, maltose, lactose) may form haemoglobin adducts and other amino groups (α-chain N-terminal, various ε-amino groups on both the α and β chains) can be glycated [6]; these adducts contribute to the measurement of total HbA_{1c}.

Clinical drivers for standardization of HbA_{1c}

Early studies indicated that monitoring of HbA_{1c} allowed changes in therapy and subsequent reduction of measured HbA_{1c}, but did not categorically show that these changes improved overall outcomes [7]. The lack of standardization, both in terms of analytical performance and clinical utility, meant there were no uniform HbA_{1c} target values for maintaining blood glucose; accordingly, there was no consensus on whether strict glucose targets were of benefit in improving outcomes. This changed, however, with the publication of the DCCT and UKPDS studies [8,9]. These large longitudinal studies, involving people with type 1 diabetes and type 2 diabetes, respectively, addressed the question of whether tight management of glucose levels resulted in a decrease in complication rates.

The DCCT study was a multicentre, randomized clinical trial in people with type 1 diabetes. The study was designed to assess if intensive therapy could be used to prevent or delay the progression of early vascular or neurological complications, using retinopathy as the primary study outcome. The treatment goal for the conventional therapy group was an absence of symptoms attributable to glycosuria or hyperglycaemia, whereas the intensive therapy group targets were near-normal glucose levels. The primary outcome measure of the study was a sustained change in levels of retinopathy; over the mean follow-up period of six years, the intensive therapy reduced the adjusted mean risk by 76% ($p < 0.001$).

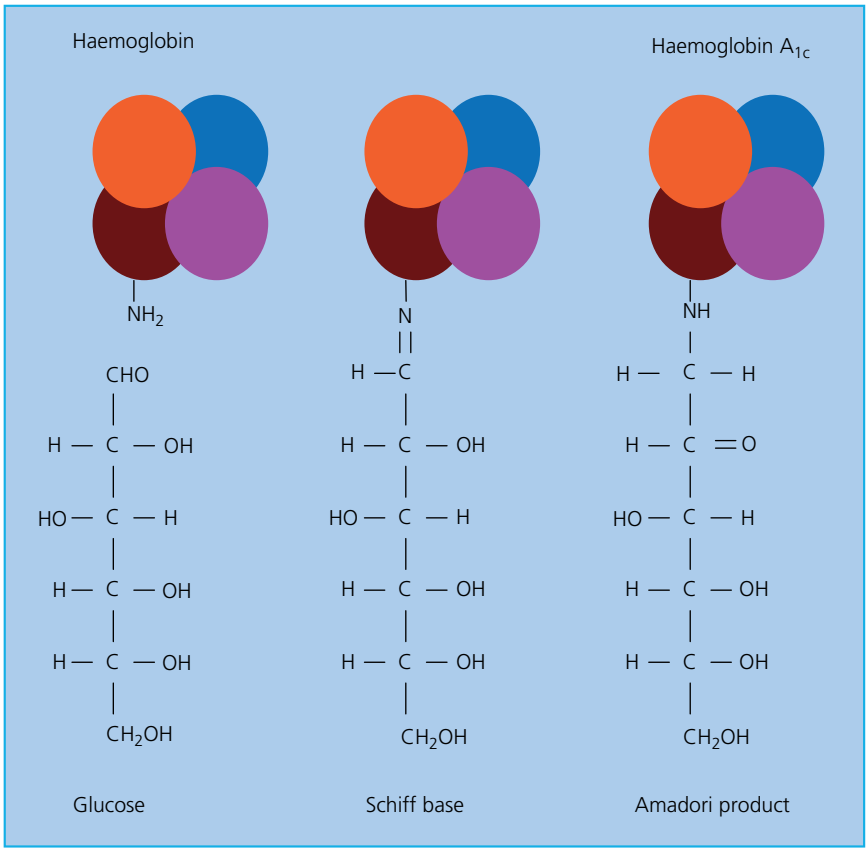

Figure 29.1 The Amadori reaction.

The EDIC study followed the individuals enrolled in the DCCT study for a further 20 years, with no attempt to formally continue the original therapy regimens of the DCCT study. Mean HbA_{1c} values converged between the two groups as a result of the changes in clinical practice brought about by the results of the original trial. The EDIC follow-on study showed that the reduction in risk for any fatal and non-fatal cardiovascular disease event (including confirmed angina, or the need for coronary artery revascularization) was 42% in intensive versus conventional treatment groups and 5% in fatal and non-fatal myocardial infarction and stroke [10].

The UKPDS study recruited individuals with newly diagnosed type 2 diabetes who were randomized by weight, then into conventional and intensive therapy regimens [9]. The conventional regimen aimed to avoid marked hyperglycaemia (fasting plasma glucose >15 mmol/l and/or symptoms of hyperglycaemia) and was primarily based on diet and lifestyle advice alone. The intensive therapy group aimed to achieve a fasting plasma glucose <6.0 mmol/l with treatment using insulin or sulfonylureas. Unlike the DCCT study, a target value of HbA_{1c} was not assigned in either of the therapy groups. In regard to the study endpoints, the reduction in microvascular complications was the most significant with a reduction of 25% in the intensive therapy group, predominantly attributable to retinopathy (two-stage progression of disease).

After the completion of the UKPDS, the individuals continued to be monitored in a follow-up study to determine if there were longer-term effects of the therapy regimens [11]. The follow-up showed a 24% risk reduction in microvascular complications, 15% risk reduction in myocardial infarction, and 13% risk reduction for all-cause mortality. This risk reduction, despite the loss in differences of HbA_{1c}, has been termed the *legacy effect*. When the relative risk profiles for micro- and macrovascular complications are compared, they show a significantly different profile: higher HbA_{1c} values contribute to a greater proportional risk in cases of microvascular disease, but a wider range of HbA_{1c} (including lower 'non-diabetic') values contribute to increased risk in macrovascular disease.

These two seminal trials showed that early, intensive therapy could significantly reduce the risk of a range of complications, even after the initial therapy has been discontinued. Accordingly, these studies established precise target HbA_{1c} values for treatment goals. This led to the urgent need for standardization of HbA_{1c} measurement for treatment targets to be globally applicable.

The lack of international standardization led to the development of national schemes for harmonization of HbA_{1c} results. The most commonly known is the US National Glycohemoglobin Standardization Program (NGSP), which uses the method utilized during the DCCT as a primary reference method. While this allowed reference to DCCT values, it suffered from interferences from non-HbA_{1c} components and there is no primary reference material.

In 1995 the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) established a working group with the remit of achieving uniform international standardization of HbA_{1c} [12]. In 1997 an international network of reference laboratories was formed to implement the newly devised reference measurement procedure for HbA_{1c}. Inter-comparison studies demonstrated a stable relationship between the IFCC reference measurement procedure and national harmonization schemes, allowing for the development of master equations to allow conversion between the more accurate IFCC values and national harmonization schemes such as the NGSP [13]. Due to difference in values between the systems, the decision was also made to adopt SI units for HbA_{1c} to avoid confusion of apparently lower HbA_{1c} values and subsequent risk of misinterpretation of results, with the introduction of standardized values. The change of units also reduced potential confusion between reports of blood glucose levels in mmol/l and HbA_{1c} measurements. By contrast, in countries that still use mg/dl, the potential for confusion increased and this is one of the reasons why the American Diabetes Association (ADA) has not adopted the new units. Nevertheless, there is an ongoing need for a considerable education initiative to inform both people with diabetes and clinicians of the change.

The international reference network for HbA_{1c} standardization has now been established for nearly two decades and is the only recognized international system to which all manufacturers of HbA_{1c} test devices should be calibrated. Many of the secondary reference methods used by the IFCC network for assigning values to calibrator materials are also the NGSP secondary reference methods; this ensures that the master equation between the two systems remains stable and that measured HbA_{1c} values can be converted from SI units to % for those who still wish to understand the values in DCCT/UKPDS terms. Master equations for the conversion between IFCC and NGSP units are as follows:

$$\text{NGSP}(\%) = \left[0.0915 \times \text{IFCC}(\text{mmol/mol})\right] + 2.15$$

$$\text{IFCC}(\text{mmol/mol}) = \left[10.93 \times \text{NGSP}(\%)\right] - 23.50$$

The global consensus statement on HbA_{1c} states that HbA_{1c} results are to be reported by clinical laboratories worldwide in SI units (mmol/mol – no decimals) and derived NGSP units (% – one decimal), using the IFCC–NGSP master equation (DCCT units) [1]. The conversion equation is available on numerous websites and in other publicly available resources.

Diagnosis of type 2 diabetes using HbA_{1c}

The successful implementation of standardization of HbA_{1c} measurement paved the way for HbA_{1c} to be introduced for the diagnosis of type 2 diabetes [14]. An International Expert Committee, appointed by the ADA, the International Diabetes Federation (IDF), and the European Association for the Study of Diabetes (EASD), published a report in 2009 recommending the use of HbA_{1c} for the diagnosis of diabetes [15]. Based on the evidence that HbA_{1c} level correlates with adverse disease outcomes and the fact that HbA_{1c} targets are used for individual treatment, use of HbA_{1c} as a diagnostic tool seemed a logical progression. The committee proposed a diagnostic cut point of 48 mmol/mol (6.5%) HbA_{1c}. In 2011 the World Health Organization (WHO) also endorsed the use of HbA_{1c} for the diagnosis of type 2 diabetes, stating:

> *HbA_{1c} can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardized to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement. [14]*

Assays for measurement of HbA_{1c}

There are a wide range of methods used for the routine analysis of HbA_{1c}. They can be divided into methods that are based on charge differences, including cation-exchange high-performance liquid chromatography (HPLC) and capillary electrophoresis, and those that separate based on structural differences such as enzymatic, immunoassay, and boronate affinity separation methods. The analytical

performance goals for all methods have been defined and are based on sigma metrics. This allows both analytical imprecision and bias to be considered together, through a measure of total analytical error [16]. Quality targets are necessary for HbA_{1c} measurement, as the difference between HbA_{1c} values considered low risk for diabetes and the level diagnostic of diabetes is very small. In some countries this range is as low as 42–48 mmol/mol, meaning that relatively small levels of bias and imprecision can have a significant impact on a clinical diagnosis. For example, if a person's true HbA_{1c} value were 45 mmol/mol, a positive or negative bias of 2 mmol/mol and imprecision of 3% could easily generate values in the diagnostic range for diabetes or the low-risk range, respectively. Since the publication of these goals, there has been annual monitoring of laboratories around the world through national External Quality Assessment (EQA) schemes. The number of laboratories that participate in the $EurA_{1c}$ trial is steadily growing, with >5000 participants within five years of the study commencing. The data generated give an overview of performance by country and by manufacturer, allowing targeted quality improvement measures to be devised and implemented [17].

Point-of-care HbA_{1c}

Point-of-care test devices are often considered a valuable addition to a clinician's armament in managing diabetes. They play an increasingly important role in wide range of clinical settings and there is increasing desire from clinicians to have access to more point-of-care tests [18]. Point-of-care testing is promoted as enabling faster clinical decision making, increased rapport with people with diabetes, and reduced referrals to secondary care and subsequent healthcare costs. However, there are also perceived barriers to implementation of point-of-care testing, including test accuracy, impact on individual pathways, and cost of testing [19].

Evidence of clinical utility for point-of-care testing for HbA_{1c} is mixed with some analyses suggesting a clear benefit, while others found an absence of clinical evidence for the use of point-of-care tests in clinical care [20, 21]. It is clear that there is a potential role for point-of-care testing; however, the accuracy, clinical utility, impact on care pathways, and cost of point-of-care testing should be considered before implementation.

The availability of point-of-care test devices for HbA_{1c} is rapidly expanding and while a small number of manufacturers currently hold market share, the number of providers is set to grow. Several studies have studied the accuracy of point-of-care test devices for HbA_{1c} and there are mixed results in performance [22]. Some devices have been extensively evaluated and can perform to the same level as laboratory devices. In future, pre-qualification of HbA_{1c} point-of-care test devices by the WHO will aid in decision making about the use of these devices more widely in clinical practice.

Factors affecting HbA_{1c} measurement

Both analytical and biological factors affect the measurement of HbA_{1c}. The importance of standardization and excellent analytical performance has already been described; however, there are a number of other factors that may lead to erroneous results in HbA_{1c} measurement (Table 29.1).

Accurate interpretation of HbA_{1c} requires a normal lifespan of erythrocytes. The presence of a shortened lifespan, for example with haemolytic disease or blood loss, can lead to underestimates of the true value. By contrast, iron-deficiency anaemia, which is associated with a longer lifespan, can be associated with an overestimate of the true value [23].

Table 29.1 Conditions that can affect the measurement of glycated haemoglobin (HbA_{1c}).

Haemoglobinopathies
Iron deficiency
Chronic kidney disease stage 4 and above
Ethnicity
Blood transfusion
Haemolysis (haemolytic anaemia)
Polycythaemia
A wide range of drugs including those use to treat HIV infection

Approximately 7% of the global population has a haemoglobin variant and these present both biological and analytical issues. The most common haemoglobin variants, in descending order of prevalence, are HbS, HbE, HbC, and HbD. Heterozygous carriers of these variants are often asymptomatic and generally have normal red-cell lifespans. There is no clear evidence on whether the structural changes in haemoglobin, due to the variants, directly affect glycation of the β chain at the N-terminal valine (to form HbA_{1c}); however, it is reasonable to assume that substitutions at the glycation site could alter the rate of glycation. Caution should be used when interpreting HbA_{1c} results from individuals with HbSS, HbCC, and HbSC, as the pathology of these diseases leads to anaemia, increased red-cell turnover, and transfusion requirements, which have adverse impacts on HbA_{1c} as a marker of long-term glycaemic levels. Alternative tests such as glycated serum protein (fructosamine) or glycated albumin should be considered for these individuals.

Some methods, such as ion-exchange chromatography and capillary electrophoresis, are capable of identifying the presence of a haemoglobin variant while others do not. Some methods are affected by haemoglobin variants and will give erroneous results. There is no set rule as to which method will or will not be affected by each variant, although the NGSP provides an updated list of methods and how they perform with common variants [24]. Some laboratories routinely report the identification of new variants; it is important to liaise with your local laboratory to assess the impact of potential variants on the local clinical population.

Chronic kidney disease affects 9% of the global population and has historically been cited as a cause of erroneous HbA_{1c} results due to the increased carbamylation of haemoglobin from uraemia. Modern HbA_{1c} methods are generally not affected by increased carbamylated haemoglobin and thus this is no longer a clinical issue. However, there is still a statistically significant divergence between HbA_{1c} values and fasting plasma glucose with increasing chronic kidney disease stages. Diabetes is a leading cause of chronic kidney disease and the two are often present concomitantly.

Studies so far suggest that chronic kidney disease stages 1–2 appear not to have a significant impact on HbA_{1c}, but chronic kidney disease stages 4–5 are consistently reported to influence HbA_{1c}, thus limiting its use in these stages. Most studies show that HbA_{1c} is underestimated compared to other markers of glycaemia either before or after the use erythropoiesis-stimulating agents. Likewise, underestimation of HbA_{1c} is observed in individuals on dialysis, either haemodialysis or peritoneal dialysis. Nonetheless, despite the high prevalence of chronic kidney disease, little evidence of the effect of chronic kidney disease stages 3–4 on HbA_{1c} is available and, in particular, on the role of anaemia, which is a common

comorbidity. Individuals with diabetes and chronic kidney disease often develop anaemia, which can lead to increased HbA_{1c} values due to erythropoietin deficiency and iron-deficiency anaemia (through elongation of the erythrocyte lifespan) or decreased HbA_{1c} caused by reduced red blood cell survival, increased erythrocyte turnover, or administration of erythropoietin. Non-iron-deficiency anaemia, if present, may falsely decrease HbA_{1c} levels. Health professionals should be aware of these erroneous results when monitoring glycaemic levels or when using HbA_{1c} for diagnosis of type 1 diabetes.

Several studies report an increase in HbA_{1c} with increasing age, with mixed opinion as to whether this is a glucose-dependent or -independent process. Increases in HbA_{1c} may simply reflect a decline in glycaemia over time; however, there is evidence to suggest that the change in HbA_{1c} is not simply related to a change in glycaemia alone and that HbA_{1c} increases with age independent of glycaemia. The discordance between glucose and HbA_{1c} is more apparent between the two-hour glucose of an oral glucose tolerance test. While the overall increase in HbA_{1c} per decade is small, when considering this over a range of 70 years the absolute difference can be clinically meaningful.

Since the introduction of HbA_{1c} for the diagnosis of type 2 diabetes, there have been numerous studies that have shown that HbA_{1c} and fasting plasma glucose identify different populations. While there is considerable overlap between the two groups, there are still people who will be diagnosed with type 2 diabetes with one method but not the other. Some of the discrepancy is due to differences in ethnicity. A recent random effects meta-analysis of multiple studies demonstrated that HbA_{1c} ranged from 1.1 to 3.0 mmol/mol lower in White populations compared to Hispanic, East Asian, Black, and South Asian populations. However, it remains unclear whether there should be differentiated HbA_{1c} diagnostic thresholds for type 2 diabetes for different ethnic groups based on risk of clinical complications. Policy makers and clinicians should be aware of the evidence indicating racial or ethnic differences when delivering a more personalized medicine approach.

Fructosamine and glycated albumin

Fructosamine is the generic name for plasma protein ketoamines. Albumin is the predominant plasma protein and constitutes a significant proportion of the fructosamine value. Fructosamine reflects the average glycaemic exposure of the preceding 1–3 weeks. It may be useful in individuals where the measurement of HbA_{1c} is precluded, for example in pregnancy where glucose levels change rapidly, or in the preconception period where motivation to improve glycaemia is high and the changes can be evaluated at shorter intervals. Fructosamine measurement is not appropriate for routine use because the assay is markedly affected by excessive turnover or excretion of albumin in, for example, renal disease. Data are currently limited on the correlation between fructosamine and HbA_{1c}, with wide confidence intervals around the diagnostic cut point of 48 mmol/mol and no direct outcome data linking fructosamine and diabetes-related complications [25]. Indirect linkage via comparison with HbA_{1c} is of limited value at this stage and further work is needed to improve its clinical utility.

Glycated albumin is the most abundant glycated serum protein and has been advocated as a more sensitive marker of glycaemia than fructosamine due the reduced heterogeneity of the lifespan of the protein. While fructosamine levels tend to decrease in the third trimester of pregnancy, due to the dilutional effects of an increased blood volume, glycated albumin levels tend to remain relatively constant in women without diabetes, because it is measured as a ratio of glycated to total serum albumin.

Albumin has a shorter lifespan in comparison to erythrocytes (~20 days). Therefore, glycated albumin is a better measure of shorter-term glycaemic levels than HbA_{1c} and is more likely to be affected by rapid fluctuations in blood glucose levels; this means that it may better reflect post-prandial increases in plasma glucose in comparison to HbA_{1c}. To date there is increasing evidence of the correlation of glycated albumin and HbA_{1c} values especially in diabetes, but there is currently limited translation of this into a marker of complications. As such, glycated albumin may be a useful marker in individuals where HbA_{1c} cannot be used. Methods for glycated albumin have now been harmonized and are relatively well characterized, meaning they may become an increasingly useful tool in the management of people with diabetes.

Measurement of blood glucose

The measurement of glucose is used for both diagnosis and monitoring of diabetes. Glucose measurement can enable the diagnosis of diabetes, impaired glucose tolerance, or impaired fasting glycaemia; the latter two are intermediate states of abnormal glucose metabolism that exist between normal glucose homeostasis and the overt hyperglycaemia of diabetes. Analysis of glucose in a blood sample is performed either in a clinical laboratory or by point-of-care testing (either by people with diabetes themselves or by healthcare professionals at the bedside or in clinic). Blood glucose measurement is a term that is frequently used without precise definition. Measurement of glucose levels is usually carried out on either capillary or venous specimens of blood; serum analysis is less common. Under usual circumstances, the concentration of glucose in whole blood is ~10–15% lower than in plasma. This is because a given volume of red blood cells contains less water than the same volume of plasma. Capillary blood glucose concentrations are very similar to venous blood levels in the fasting state; however, after a glucose load capillary samples may be up to 25% higher than simultaneously drawn venous blood samples [26]. Table 29.2 shows the equivalent measurements from the different sample types.

Blood glucose levels are expressed in SI units as millimoles/l (mmol/l). The traditional unit for measuring blood glucose is milligrams/decilitre (mg/dl), although use of these units is now largely confined to the USA. To convert mmol/l glucose to mg/dl, multiply by 18 (Table 29.2). Blood specimens for analysis of glucose levels need to be taken under controlled conditions as they are subject to

Table 29.2 Differences in blood glucose values dependent on sample type.

	Glucose concentration (mmol/l)[a]			
	Plasma		Whole blood	
Time of measurement	Venous	Capillary	Venous	Capillary
Fasting	≥7.0	≥7.0	≥6.1	≥6.1
2 h after a glucose load	≥11.1	≥12.2	≥10.0	≥11.1

[a] 1 mmol/l = 18 mg/dl.

continuing glycolysis by red blood cells, which is enhanced by the presence of leucocytosis. The continuing glycolysis should be avoided by collection onto ice, rapid centrifugation, and analysis within 30 minutes [27]; however, this is impractical in many routine clinical settings. The use of blood collection tubes containing sodium fluoride inhibits further glucose metabolism, although there is still some loss of glucose for the first two hours post-collection, when the amount of glucose lost could be as much as 15% of the original concentration. If an individual has an intravenous line *in situ*, blood should be drawn from the arm opposite to the one with the line to prevent contamination of the sample from any infusion. Clinicians should be aware of these potential limitations of blood glucose measurement.

There are three basic approaches to the laboratory measurement of blood glucose concentration: reducing methods, condensation methods, and enzymatic methods. Most laboratories utilize hexokinase and glucose oxidase enzymatic methods, with only a small proportion of laboratories using glucose dehydrogenase methods. Reducing methods and condensation methods are cheaper than enzymatic methods, but they are more prone to interferences from strong reducing agents or other sugars.

Point-of-care test devices for blood glucose

Glucose oxidase and glucose dehydrogenase methods are those most commonly used in handheld point-of-care test devices. Most systems include strips that contain all the reagents necessary for analysis in a single-use disposable unit. Blood is applied to the end of the strip either directly or through capillary action by touching the strip to the blood droplet being analysed.

Some meters additionally incorporate the facility to measure blood ketone levels, of particular importance for people with type 1 diabetes. Other meters have the facility to calculate insulin bolus requirements or to download blood glucose results for evaluation of the pattern of glucose levels over time.

Most of the currently marketed handheld capillary blood glucose meters give results as an equivalent to venous plasma glucose, but this is not always the case. The same type of handheld meter may be calibrated to report whole blood glucose in one country and plasma values in another. The calibration of a meter should be checked and the thresholds for action set accordingly. Factors that affect the accuracy of point-of-care test devices for blood glucose are shown in Table 29.3.

Table 29.3 Factors that affect the accuracy of point-of-care test devices for blood glucose.

- Direct chemical interferences with substances such as acetaminophen and ascorbate (vitamin C)
- Blood oxygen concentrations in systems using glucose oxidase
- Changes in blood viscosity and haematocrit
  - Oedema
  - Dehydration
  - Hyperosmolar hyperglycaemia syndrome
  - Sepsis
  - Poor sampling by massaging sample site
- Errors arising from transcription errors (when not electronically linked)
- Impact of environmental conditions
  - Temperature
  - Humidity
  - Altitude

Point-of-care testing, utilizing capillary blood glucose measurement, can be used to replace venepuncture in many settings, with greater comfort and more rapidly available results for monitoring individuals in an acute situation. Standards have been laid down to ensure that bedside glucose determinations can be made accurately and include the need for well-defined policies, which incorporate adequate training, quality control procedures, and regular maintenance of equipment [28]. This guidance differs from that provided for devices that are intended for self-monitoring of blood glucose by individuals with diabetes.

Self-monitoring blood glucose devices

Devices used for self-monitoring of blood glucose must meet ISO 15197:2013 standards; in addition other standards may be dictated by national or local guidance. It is of note that people with diabetes often assume that their devices are accurate because they meet the standards prescribed or carry approval from the US Food and Drug Administration (FDA) or the European Conformité Européenne (CE) mark, although this is not always the case and education plays a key role in supporting people with diabetes to identify incorrect data from their device [29]. Despite their imprecision, blood glucose meters remain particularly helpful at higher blood glucose values, where, for example, it is of less importance to distinguish a plasma glucose of 11 mmol/l (198 mg/dl) from one of 14 mmol/l (252 mg/dl). In such circumstances, the aim of management is to achieve a substantial reduction in plasma glucose. At lower plasma glucose levels, however, the consequences of imprecision of 15% are much greater.

Accuracy of devices is dependent on both the user and the device, therefore evaluation of the individual's technique when using their device is advised at regular intervals. Correct sampling for self-monitoring of blood glucose devices is important for accurate results and is detailed in information for users for each device, as well as in publications such as the WHO Guidelines on Drawing Blood (Figure 29.2) [30]. The most common site of sampling is the pad of the finger; alternative sites for sampling include the base of the thumb, forearm, and thigh. Pre-meal readings will be the same between sites, but at times of rapid glucose change

Figure 29.2 The correct technique for self-monitoring of blood glucose improves the accuracy of testing.

(in the post-prandial period or during hypoglycaemia), forearm and thigh results will be different from fingertip results, because glucose changes lag behind the fingertip results.

Newer devices can store and upload data to mobile devices or computers, may allow reapplication of blood to the sample strip if the first sample is insufficient, and utilize very small volumes of blood. This allows for smaller, thinner lancets to be used, which reduces discomfort for the individual and encourages ongoing testing. Calibration and issues such as erroneous readings when test strips are incorrectly inserted have largely been ameliorated with updates in technology and thus further reduce the risk of errors.

Continuous glucose monitoring

CGM devices use a broad range of analytical techniques to assess glucose levels. The development of these devices has arisen from the increasing awareness of the need for individuals to have optimal glycaemic levels. CGM devices use a range of techniques, from predominantly non-invasive through to invasive methods. All of these devices work on the sampling of interstitial fluids on the basis that this correlates with blood glucose levels. For further details refer to Chapter 32.

Estimated average glucose

Estimated average glucose (eAG) values have been derived from the correlation between mean HbA_{1c} levels and mean blood glucose levels in the A_{1C}-Derived Average Glucose (ADAG) study [31,32]. The mean glucose levels were determined from self-monitoring of blood glucose and CGM measurements and calculated by combining weighted results from at least two days of CGM performed four times, with seven-point daily self-monitoring of capillary glucose performed at least three days per week. Numerous calculators are available online for the calculation of estimated average glucose from HbA_{1c}. The ADA and the American Association for Clinical Chemistry have determined that the correlation in the ADAG data is strong enough to justify inclusion in the Standards of Medical Care in Diabetes [33]; however, this is not a universally accepted calculation due to the wide range in glucose levels reported for each HbA_{1c} level.

Measurement of glucose in urine

The presence of glycosuria can be identified by semi-quantitative or quantitative glucose methods. The use of dry reagent test strips for urine dipstick analysis allows cheap, rapid, and portable urine analysis. Urine specimens should be analysed immediately, preserved at pH <5 to inhibit bacterial metabolism or stored at 4 °C. Chemical reactions and subsequent visual assessment of the colour against a printed colour chart yield a semi-quantitative result. As a consequence of their condition, many people with diabetes are prone to visual difficulties and this has been a major operator-dependent step with visually monitored systems, in particular distinguishing the small variations in blues and blue-green colours produced by many of the test strips. Automated urinalysis machines are now available that can accurately determine colour changes in samples, making them a cheap and rapid method for screening large numbers of samples. Quantitative methods utilize hexokinase or glucose dehydrogenase methods.

The clinical utility of urine glucose measurement is limited, as it does not reflect the changing levels of hyperglycaemia with any accuracy. In addition, the renal threshold above which glucose is excreted in the urine varies between individuals and during pregnancy and with ageing. Nevertheless, it may have a role in resource-poor settings where identification and treatment of individuals with suboptimally managed diabetes are the highest priority.

Measurement of ketones

Diabetic ketoacidosis (DKA) is a commonly encountered diabetes-related emergency with appreciable morbidity and mortality. Reports of euglycaemic DKA in people with diabetes using sodium-glucose cotransporter 2 (SGLT-2) inhibitors means that clinicians and people with diabetes should be aware of the possible testing options [34]. Ketone bodies are derived from the catabolism of free fatty acids to form acetoacetate, acetone, and β-hydroxybutyrate. Acetoacetate and β-hydroxybutyrate are normally present in equimolar concentrations; however, due to increased levels of nicotinamide adenine dinucleotide + hydrogen (NADH) present in severe diabetes, the ratio may shift towards β-hydroxybutyrate up to 6:1, and thus methods for ketones that only detect acetoacetate may significantly underestimate the degree of ketosis. Therefore, methods that measure β-hydroxybutyrate are preferable in the monitoring of individuals with DKA. Like all laboratory and point-of-care testing methods, rigorous quality assurance procedures should be in place, along with training of users to understand the limitations of the devices and where to seek help and advice in their use.

Clinical approaches to monitoring in diabetes

Effective monitoring of glycaemia requires a partnership between healthcare professionals and the person with diabetes. Optimal testing intervals and the balance between use of laboratory testing and self-monitoring require consideration of a range of factors, extending from wholly clinician-directed testing (e.g. during acute illness in a hospital setting) to self-monitoring by a person with diabetes in the community who is otherwise well. The approach to this discussion with people with diabetes should be person centred and communication should be strength based, with a focus on active listening to ensure that the individual's beliefs, abilities, and barriers to care can be fully considered. As well as person-centred communication, care should be offered from multidisciplinary teams to present a holistic approach to treatment.

Self-monitoring of blood glucose

Self-monitoring of blood glucose, in conjunction with diabetes self-management education and support, is an integral part of self-care for people with type 1 diabetes to maintain levels of blood glucose that minimize risks of complications. In addition, it is required for people with type 2 diabetes using insulin, and for some people with type 2 diabetes who have specific indications [35,36]. When correctly done, glucose monitoring enables people with diabetes to assess their individual response to therapy and provide insight into their achievement of their target goals. The ability to accurately record data from self-monitoring of blood glucose devices in the

individual's records enables more effective diabetes management and guides medical nutrition therapy, physical activity, identification of risk of hypoglycaemia, and adjustment of medications (particularly prandial insulin doses). The individual's specific needs, capabilities, and goals should dictate the frequency of self-monitoring of blood glucose and timing or the consideration of CGM use. For further detail on testing using CGM including frequency, refer to Chapter 32.

Monitoring in type 1 diabetes

Glycaemia should be assessed using HbA_{1c} measurement in all adults with type 1 diabetes every 3–6 months. This could be increased if a person's blood glucose is thought to be rapidly changing due to treatment changes or when they are not meeting their treatment goals [33, 37]. As detailed in the previous sections, HbA_{1c} methods should be calibrated to the IFCC standardization and enrolment in an EQA scheme is strongly recommended. In the USA and some other countries, methods are also expected to be certified by the NGSP. Targets for HbA_{1c} vary between different guidelines and are dependent on multiple factors. Goals are set to minimize risk of long-term complications, but individualized targets should be agreed based on lifestyle and previous experience of hypoglycaemia. HbA_{1c} values of 48 or 53 mmol/mol (6.5% or 7.0%) are common goals, although these may differ in older adults and those with multiple comorbidities [33, 37].

Adults with type 1 diabetes should also be encouraged and supported to routinely undertake self-monitoring of blood glucose, and test at least four times a day (including before each meal and before bed). This may be increased to up to ten times a day when treatment goals are not being reached, when hypoglycaemic episodes are increasing in frequency, when the individual's employment or legal restrictions require it, during increased activity, or during periods of illness. The use of CGM devices for monitoring is becoming increasingly common.

Education is an essential tool to empower individuals with diabetes to monitor their blood glucose, and they should be taught how to use the blood glucose data to adjust food intake, exercise, or pharmacological therapy to achieve specific goals. However, tight glucose levels bring with them the risk of hypoglycaemia, which in turn may occur more frequently in people with suboptimally managed diabetes [38]. Additional checks on blood glucose levels should be made in relation to the risk of hypoglycaemia, for example before exercise or driving and in the presence of symptoms that may indicate hypoglycaemia.

Targets for blood glucose level vary between different guidelines. The ADA guidance recommends pre-prandial capillary plasma glucose of 4.4–7.2 mmol/l (80–130 mg/dl) and peak post-prandial capillary plasma glucose of 10.0 mmol/l (<180 mg/dl) [33].

Children and young adults with type 1 diabetes and their caregivers should be given age-related and culturally appropriate education for self-monitoring of blood glucose. Guidance on frequency varies from a minimum to five times a day and upwards; CGM is also advocated [39]. Glucose concentration targets are similar to those of adults; however, HbA_{1c} targets vary more widely depending on the source of the guidelines.

Guidance for monitoring diabetes in a hospital setting varies depending on the guideline and the resources available; the following is a representative example. Blood glucose levels for critically ill individuals should be maintained between 7.8 and 10.0 mmol/l (140 and 180 mg/dl), although a lower target of 6.1–7.8 mmol/l (110–140 mg/dl) may be aimed at, provided that there is no increase in the incidence of severe hypoglycaemia [40]. Self-management of diabetes in the hospital setting may be appropriate where adult individuals are alert, able to self-manage their diabetes at home, and have stable requirements for insulin. This may also offer an opportunity for providing support in learning techniques of insulin adjustment in line with carbohydrate intake.

Monitoring in type 2 diabetes

For people with type 2 diabetes, the overall level of glycaemia should be monitored using HbA_{1c} every 3–6 months until stable and there is no change in therapy. For those with stable blood glucose levels and no changes in therapy, every 6 months is sufficient. The majority of HbA_{1c} values are still provided via centralized laboratories; however, there is increasing interest in the use of point-of-care test devices to enhance community-based care pathways. Currently there is no guidance that actively supports routine use of point-of-care HbA_{1c} for diagnosis of diabetes, although there are examples of effective use of point-of-care HbA_{1c} in the community-based care of people with type 2 diabetes, such as the Norwegian Organization for Quality Improvement of Laboratory Examinations (Noklus) system [41].

Setting HbA_{1c} targets for people with type 2 diabetes is important to guide decisions about treatment and to provide feedback to the individual and clinician about the effectiveness of treatment. The level at which targets should be set for an individual remains widely debated. Although guidelines provide advice about generally accepted targets, individuals need to be involved in decisions about their own HbA_{1c} target. Once available, the results of tests should be used to encourage people to achieve and maintain their target unless they develop hypoglycaemia.

If HbA_{1c} measurement is unavailable, then a fasting plasma glucose measurement can be used to indicate need for, or response to, a treatment that leads to a reduction in fasting hyperglycaemia (e.g. metformin or a sulfonylurea). A fasting capillary plasma glucose level of 3.9–7.2 mmol/l is recommended as a target.

The approach to self-monitoring of blood glucose in people with non-insulin-treated type 2 diabetes is mixed. Guidelines for treatment of people with type 2 diabetes draw attention to the lack of evidence for effectiveness and cost-effectiveness of routine use of self-monitoring of blood glucose and recommend that it should not be routinely used. Although there is some evidence that testing may improve glycaemic levels in some people, there is similarly evidence that data are frequently not acted on and that the benefit does not outweigh the cost. It continues to have a place where there are concerns about hypoglycaemia (e.g. use of sulfonylurea) or HbA_{1c} measurements are not possible or do not provide an accurate measure of glycaemia.

For people with type 2 diabetes who are using insulin, self-monitoring of blood glucose is needed to adjust insulin dose and check that glucose levels are maintained, although optimal use remains to be established. Frequency and targets are similar to those with type 1 diabetes.

Diabetes in pregnancy

Diabetes in pregnancy and gestational diabetes (diabetes first identified during pregnancy) are rising in prevalence. Pre-conception care for women with diabetes is important, with glycaemic targets as near normal as possible (HbA_{1c} <48 mmol/mol [<6.5%]) to reduce the risk of complications during pregnancy and birth, including macrosomia, pre-eclampsia, and congenital abnormalities. The results of the Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial (CONCEPTT) demonstrated that the use of CGM was associated with improved neonatal outcomes and led to the recommendation that all pregnant women with type 1 diabetes, or those without type 1 diabetes but on intensive insulin therapy, be offered CGM [42]. Further details are provided in Chapter 71.

Monitoring of diabetes in special situations

Bariatric surgery

Bariatric surgery is being increasingly used in the management of people with type 2 diabetes and obesity. Post-surgery, blood glucose levels may return to near-normal levels for prolonged periods of time, with HbA_{1c} values within the normal range. These individuals are determined to have diabetes in remission. While each of the measures used to diagnose diabetes is valid, the preferred test for identification of diabetes remission is HbA_{1c} at <48 mmol/mol (<6.5%) for three months or more with no glucose-lowering pharmacological intervention; the same caveats to the use of HbA_{1c} for diagnosis and monitoring apply to this situation. As implied by the term *remission*, there is a need for ongoing monitoring of these people for complications of diabetes, including retinal screening, renal function, foot evaluation, and measurement of blood pressure and weight, in addition to ongoing monitoring of HbA_{1c}. The frequency of HbA_{1c} measurement should not be more often than every three months nor less frequent than yearly to confirm continuation of the remission, in line with monitoring of stable type 2 diabetes [43].

Low-resource settings

While data and guidance advocate timelines and tests for monitoring of diabetes, the management of diabetes is very costly. Estimates of test costs vary immensely, but it is unlikely that the cost of prescribed monitoring can be met in many low-resource settings. The myriad of different environmental and economic factors around the use of diabetes testing mean that testing is often suboptimal. While urine dipsticks for glucose are inexpensive and portable, they are non-specific, non-quantitative, and not sensitive to small changes in blood glucose levels. Blood glucose testing necessitates adequate fasting and temperature-sensitive reagents, and CGM devices are very expensive. HbA_{1c} is a preferred monitoring test as fasting is not required and it is a longer-term marker of glycaemic levels, but point-of-care test devices are still quite cumbersome and not yet truly adapted for the low-income setting. WHO and other non-governmental organizations are actively engaged with the development and assessment of point-of-care devices for diabetes testing, and this is an area that is likely to see significant investment, research, and improvement in the future.

Conclusion

Glycaemic levels should be monitored regularly for all people with diabetes. The optimal method of determining risk of long-term complications is through HbA_{1c} measurement, although if this is not available then examination of a series of blood glucose measurements, including fasting tests, may provide guidance. HbA_{1c} methods should be standardized to the IFCC reference measurement procedure and units of reporting are the SI units mmol/mol, with derived percentage units in brackets. The role of CGM in diabetes monitoring is increasing and is likely to become a prominent feature of diabetes care in the future. New considerations for diabetes monitoring, such as in the remission of diabetes post-surgical intervention, will continue to be identified, and there is a critical need for investment and research into low-cost, robust, and accurate testing for low-resource settings.

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30 Biomarkers and Precision Medicine in Diabetes

Sok Cin Tye[1], Michele Provenzano[2], and Hiddo J.L. Heerspink[1]

[1] Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[2] Nephrology, Dialysis and Renal Transplant Unit, S'Orsola Hospital - IRCCS - Alma Mater Studiorum University of Bologna, Italy

Key points

- Precision medicine is an emerging concept to personalize healthcare decision making and treatment selection according to an individual's demographic, physical, and clinical data.
- The unprecedented progress in molecular and genetic technologies has resulted in a better insight into the pathophysiology of diabetes and response to treatment.
- In monogenic diabetes where a mutation in a single gene can cause the disease, various examples of the utility of genetic-based approaches to tailor treatment are available.
- The pathophysiology and response to treatment are more complex and heterogeneous in type 2 diabetes and are determined by variations in multiple genes and other factors such as lifestyle and environment.
- Multiple factors thus have to be considered in a complex disease like type 2 diabetes when making tailored treatment choices.
- Pharmacogenetics and use of protein markers can inform precision medicine approaches for the treatment of diabetes.

Introduction

According to the International Diabetes Federation (IDF), approximately 463 million people were living with diabetes in 2019 [1]. Estimates from the IDF indicate that this number will rise to 700 million people in 2040. The commonest types of diabetes are type 1 diabetes and type 2 diabetes. Type 1 diabetes is caused by the autoimmune destruction of β cells in the pancreas, which leads to a discontinuation of insulin production [2]. Type 2 diabetes results from a combination of inadequate insulin secretion in the face of reduced insulin action. The pathophysiology is based on genetic and lifestyle factors [3]. In addition to type 1 diabetes and type 2 diabetes, monogenic varieties of diabetes exist, but their prevalence is much lower and they account for ~3% of cases of diabetes diagnosed in children [4,5].

Diabetes increases the risk of micro- and macrovascular complications. Exposure to high blood glucose levels damages the microvasculature in the kidney and eye, resulting in chronic kidney disease and blindness [6]. Diabetes-related kidney disease occurs in 30–40% of all people with diabetes and diabetic retinopathy is the major cause of blindness in adults in most countries in the world [7,8]. Cardiovascular disease is a manifestation of injury to larger blood vessels in the heart and peripheral vasculature. Cardiovascular disease occurs frequently in people with diabetes and accounts for approximately one-third to one-half of all diabetes-related deaths [9].

Diabetes, in particular type 2 diabetes, frequently clusters with other risk factors for cardiovascular and kidney disease, such as hypertension, hypercholesterolemia, obesity, and microalbuminuria [10,11]. The first aim of diabetes treatment is to correct hyperglycaemia to ameliorate diabetes symptoms, such as polyuria, tiredness, and blurred vision. Long-term treatment goals include the prevention of micro- and macrovascular complications. Landmark clinical trials have shown that intensive glycaemic management in people with type 1 diabetes and type 2 diabetes reduces the long-term risk of diabetes-related complications, including retinopathy and kidney and cardiovascular disease [12–14]. However, for the optimal prevention of long-term complications, other risk factors such as obesity, hypertension, and hypercholesterolemia should be managed as well. Blood pressure lowering with an angiotensin-converting enzyme (ACE) inhibitor confers micro- and macrovascular protection [15]. In addition, cholesterol lowering with statins decreases the incidence of cardiovascular events in people with diabetes [16]. Thus, targeting multiple risk factors simultaneously is necessary to enhance protection against micro- and macrovascular events. In the Steno 2 trial, 160 individuals with type 2 diabetes were randomly assigned to intensive multifactorial risk factor management or conventional treatment [17]. Multifactorial risk factor management significantly improved cardiovascular outcomes and during the 21-year follow-up, the risk of kidney failure or mortality was reduced by 47%, highlighting the importance of targeting multiple cardiovascular risk factors rather than glycaemic management alone [18].

Various oral anti-diabetes drugs have been developed in the last decades, including dipeptidyl-peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonist (GLP-1 RA), and sodium-glucose cotransporter-2 (SGLT-2) inhibitors. These drug classes significantly improve glycaemic levels when added to the traditionally used drugs such as metformin, sulfonylurea derivatives, and insulin. Importantly, GLP-1 RA and SGLT-2 inhibitors reduce body weight and blood pressure and improve cardiovascular outcomes. Moreover, SGLT-2 inhibitors have favourable effects beyond

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improving glucose levels: they also reduce blood pressure, body weight, uric acid, and the risks of kidney and heart failure [19–21].

Based on past trials, current clinical practice guidelines recommend monitoring and optimizing multiple cardiovascular risk factors of kidney and cardiovascular disease in people with type 2 diabetes. Most guidelines also recommend the use of GLP-1 RA and SGLT-2 inhibitors as an adjunct to metformin [22,23]. However, despite the use of these newer agents, many individuals with diabetes still experience cardiovascular and kidney diseases [24,25]. This is illustrated in well-conducted large clinical trials demonstrating that even during treatment with GLP-1 RA and SGLT-2 inhibitors, the risk of cardiovascular outcomes, heart failure hospitalizations, and kidney failure remains high (Figure 30.1) [19,20,26]. Part of the suboptimal protection can be explained by an insufficient response to the currently used drugs. For example, ~35% of treated individuals do not show a reduction in glycated haemoglobin (HbA_{1c}) in response to metformin, the first choice of glucose-lowering treatment for people with type 2 diabetes [27,28]. This variation in response is observed not only for glucose-lowering agents, but for other drugs used in the management of diabetes. For example, 35% of the treated individuals show no reduction in blood pressure to an ACE inhibitor or angiotensin receptor blocker (ARB) [29,30].

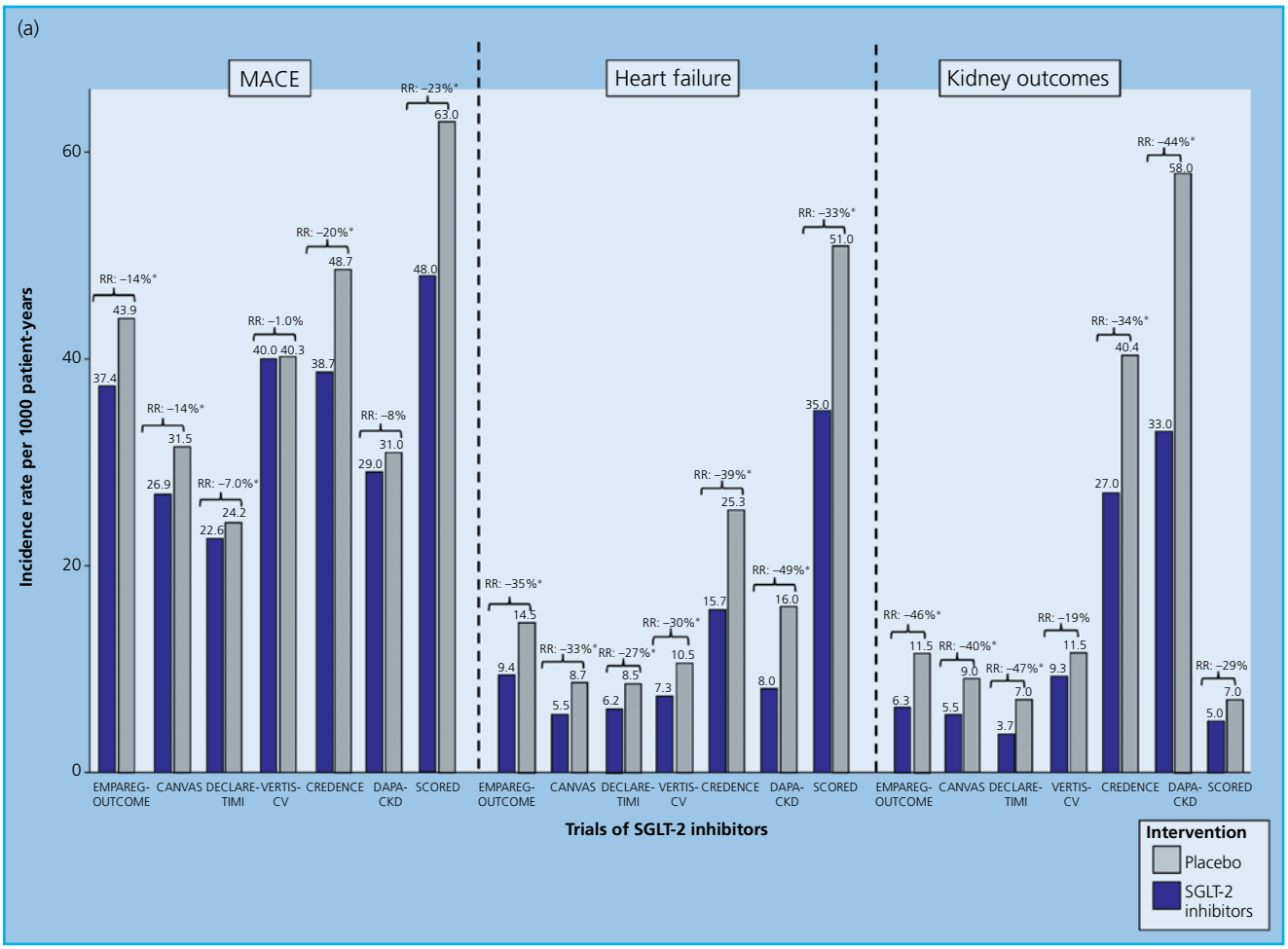

Figure 30.1 (a) Incidence rate per 1000 person-years for the occurrence of major adverse cardiovascular events (MACE), heart failure, and kidney outcomes in randomized controlled trials of the sodium-glucose cotransporter-2 (SGLT-2) inhibitors. MACE outcome is defined as a composite of death from cardiovascular causes, nonf-atal myocardial infarction, or non-fatal stroke. Heart failure outcome is defined as hospitalization for heart failure. The definition of kidney outcomes for each trial is as follows: (i) EMPAREG-OUTCOME – doubling of serum creatinine level accompanied by estimated glomerular filtration rate (eGFR) of 45 ml/min/1.73 m^2, initiation of renal replacement therapy, or death from renal disease; (ii) CANVAS – 40% reduction in eGFR, end-stage kidney disease (ESKD), or death from renal causes; (iii) DECLARE-TIMI – sustained decrease in eGFR by at least 40% to less than 60 ml/min/1.73 m^2, ESKD, or renal death; (iv) VERTIS-CV – death from renal causes, renal replacement therapy, or doubling of the serum creatinine level; (v) CREDENCE – ESKD, doubling of serum creatinine, or renal death; (vi) DAPA-CKD – composite of decline in eGFR of ≥50%, ESKD, or death from renal causes; (vii) SCORED – sustained decrease of ≥50% in eGFR from baseline for ≥30 days, long-term dialysis, renal transplantation, or sustained eGFR of <15 ml/min/1.73 m^2 for ≥30 days. * in risk reduction (RR) indicates a significant risk reduction. (b) Incidence rate per 1000 person-years for the occurrence of MACE, heart failure, and kidney outcomes in randomized controlled trials of glucagon-like peptide-1 receptor agonists (GLP-1 RAs). MACE outcome is defined as a composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke (in ELIXA* it consists of MACE and hospitalization for unstable angina). Heart failure outcome is defined as hospitalization for heart failure (in HARMONY OUTCOMES it consists of a composite of heart failure and cardiovascular death). Definitions of kidney outcomes in the other trials were (i) LEADER – new-onset persistent macroalbuminuria, persistent doubling of serum creatinine level, and eGFR of ≤45 ml/min/1.73 m^2, the need for continuous renal replacement therapy, or death from renal disease; (ii) SUSTAIN-6 – persistent macroalbuminuria, persistent doubling of serum creatinine with creatinine clearance <45 ml/min/1.73 m^2, and need for renal replacement therapy; (iii) EXSCEL – composite of 40% eGFR decline, renal replacement, and renal death; (iv) REWIND trial – development of macroalbuminuria, sustained 30% or greater decline in eGFR, or new chronic renal replacement therapy comprising dialysis or renal transplantation. * in RR indicates a significant risk reduction.

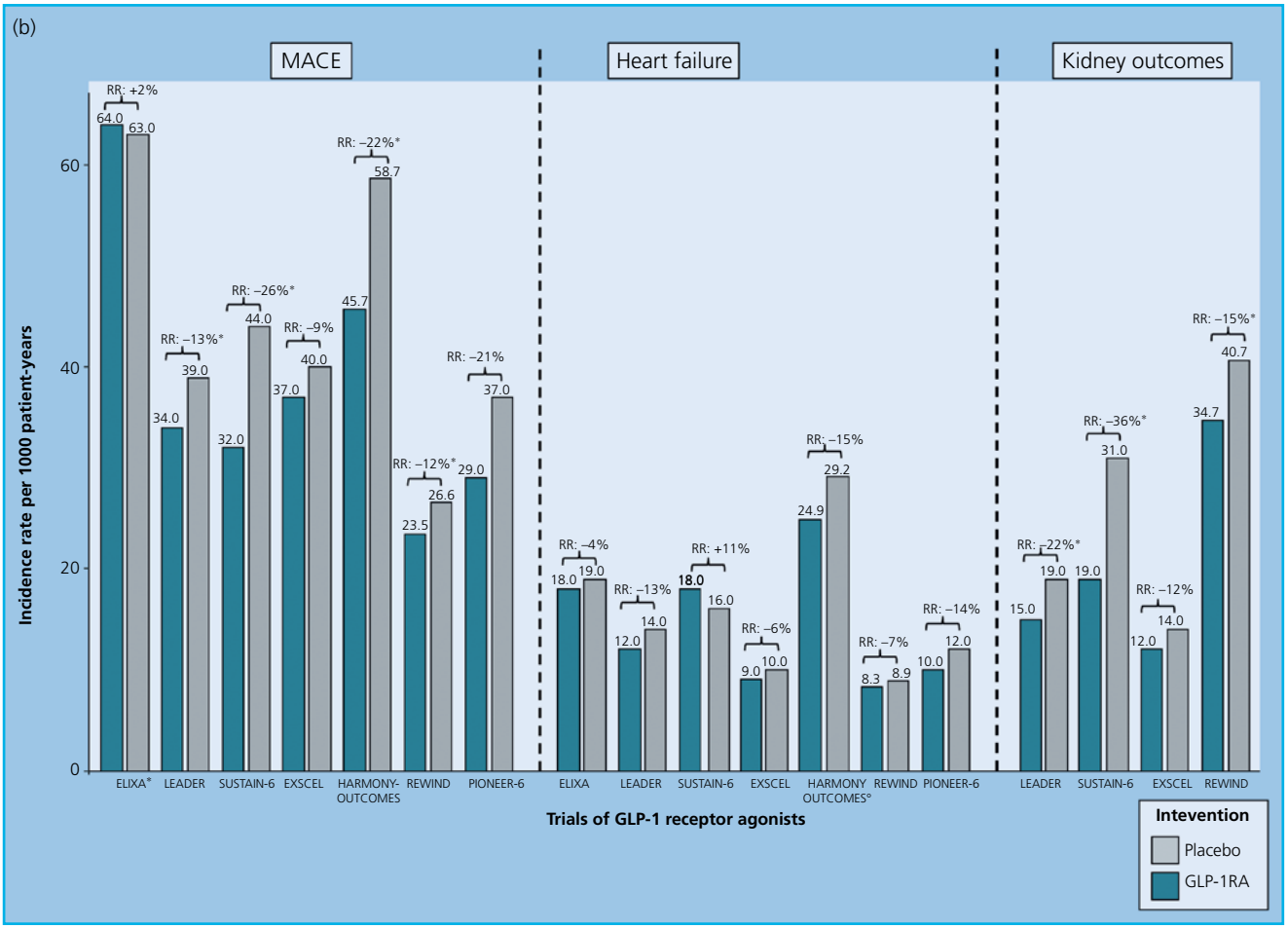

Figure 30.1 (*Continued*)

Understanding the underlying mechanisms of therapy resistance may stimulate the development of new strategies to improve the pharmacotherapy of diabetes and pave the way for more individualized and effective drug use in clinical practice.

In the past, the pharmacological treatment of diabetes used the same drugs for all people with diabetes. However, there has been significant interest in incorporating clinical laboratory data, lifestyle and environmental information, and data from human genetics in treatment decisions to individualize and tailor pharmacotherapy. More recent guidelines have started to adopt this approach and, for example, recommend individualized glycaemic targets and drug choices for subgroups of individuals [31]. Recent advances in genetics and simultaneous measurements of numerous proteins and metabolites have increased expectations that in the near future treatment decisions will be able to be further tailored to the individual based on specific personal characteristics [32–34]. This concept, which is termed *personalized medicine*, is usually defined as a medical model that separates people into different groups, with medical decisions, practices, interventions, and/or products being tailored to the individual based on their predicted response or risk of disease [35]. According to this definition, diagnostic testing is used to select the most appropriate treatment based, for example, on the genetic make-up of an individual. Furthermore, other factors, including concomitant diseases, clinical chemistry information, and lifestyle and environmental factors, are used to guide medical decision making for the individual.

In this chapter, we review the variation in drug response to commonly used drugs in people with diabetes to guide personalized treatment choices. We start the chapter with a summary of examples from monogenic diseases to illustrate how pharmacogenetics can be used to tailor therapy decisions. In the second part, we focus on oral agents for the treatment of type 2 diabetes. In contrast to monogenic diseases, the pathophysiology and response to treatment in type 2 diabetes are heterogeneous and complex, making individualized treatment more difficult. We close the chapter by summarizing the challenges and future research directions for implementing personalized medicine in clinical practice.

Precision medicine in monogenic diabetes

Monogenic diabetes due to polymorphism in a single gene accounts for 1–6% of all cases of diabetes at a young age [4,5]. The two major forms of monogenic diabetes are neonatal diabetes mellitus (NDM), which commonly manifests prior to 6 months of age, and maturity-onset diabetes of the young (MODY), which usually occurs in adolescence or early adulthood [36]. Other forms of monogenic diabetes include multisystem monogenic insulin resistance syndromes such as Alström syndrome, Bardet-Biedl syndrome, or Wolfram syndrome. Genetic polymorphisms in various forms of monogenic diabetes and their pathophysiological consequence are presented in Table 30.1 [37]. Development of targeted next-generation DNA sequencing has enabled rapid and comprehensive testing for genetic aetiologies of monogenic diabetes [38].

Table 30.1 Molecular diagnosis, pathophysiology, and treatment of neonatal diabetes and maturity-onset diabetes of the young (MODY).

Monogenic disease	Genetic polymorphism	Pathophysiology	Treatment
Subtypes of neonatal diabetes			
Transient	6q24	Abnormal β-cell function with impaired insulin secretion	Sulfonylurea derivatives, insulin
Transient	HNF1B		Insulin
Permanent	GCK		Insulin
Transient/permanent	KCNJ11		Sulfonylurea derivatives, insulin
Transient/permanent	ABCC8		Sulfonylurea derivatives, insulin
Transient/permanent	INS		Insulin
Subtypes of MODY			
Genetic polymorphism in the transcriptional factors			
MODY1	HNF4A	Pancreatic β-cell dysfunction	Sulfonylurea derivatives, insulin
MODY3	HNF1A		Sulfonylurea derivatives, insulin, GLP-1 RAs, SGLT-2 inhibitors
MODY4	PDX1/IPF1		OADs, insulin
MODY5	HNF1B		Insulin
MODY6	NEUROD1		OADs, insulin
MODY7	KLF11		OADs, insulin
MODY9	PAX4		OADs, insulin
MODY11	BLK	Impairment in insulin secretion	OADs, insulin
Mutations in glucokinase enzymes regulating glucose metabolism			
MODY2	GCK	Impairment in glucose-sensing mechanism	Treatment not required
Protein misfolding disorders			
MODY8	CEL	Defects in endocrine and exocrine pancreatic function	OADs, insulin
MODY10	INS	Structurally defective insulin molecules	OADs, insulin
Mutations in the K_{ATP} regulating insulin secretion			
MODY12	ABCC8	Impairment in insulin secretion	Sulfonylurea derivatives
MODY13	KCNJ11		Sulfonylurea derivatives
Signal transduction error			
MODY14	APPL1	Impairment in insulin secretion	OADs, insulin

GLP-1 RA, glucagon-like peptide-1 receptor agonist; K_{ATP}, potassium ATP; OAD, oral anti-diabetes drug; SGLT-2, sodium-glucose cotransporter-2.

Neonatal diabetes

About 22 genetic causes of NDM have been identified so far [39]. NDM can be subdivided into transient and permanent forms, depending on the affected gene. Individuals with transient NDM due to methylation of chromosome 6q24 tend to have hyperglycaemia, which resolves within the first year after birth, although relapses during childhood or puberty are possible [40,41]. On the other hand, diabetes does not relapse and usually persists lifelong among individuals with NDM due to gene mutations in the potassium ATP (K_{ATP}) channel KCNJ11/ABCC8/INS.

The treatment goal for all individuals with NDM comprises optimizing glycaemic levels with oral anti-diabetes agents or insulin. However, a large variation in response to these drugs exists, which is partly explained by the underlying genetic variances. Sulfonylurea derivatives, for example, act by promoting the closure of the K_{ATP} channel, thereby stimulating insulin secretion from the pancreatic β cells. The long-acting sulfonylurea derivative glibenclamide is most commonly used for NDM. Other sulfonylurea derivatives such as gliclazide, glipizide, and glimepride have been used, but were inferior to glibenclamide [42]. For individuals with transient NDM due to 6q24 methylation abnormalities, low-dose sulfonylurea derivatives are effective, whereas for those with K_{ATP} channel polymorphisms, high-dose sulfonylurea derivatives are required to optimize glucose levels [43]. With respect to insulin treatment, rapid-acting insulin (e.g. lispro, aspart, glulisine) is the first-choice agent to achieve HbA_{1c} targets [44]. There is some evidence that children with NDM and alterations in the insulin coding genes benefit most from early aggressive insulin therapy to prevent misfolding of the insulin proteins [45].

Maturity-onset diabetes of the young

MODY is a genetically heterogeneous disorder accounting for 1–5% of all diabetes cases, but often remains undiagnosed [46]. In the past, a combination of clinical factors and biomarkers was used to guide identification of individuals with MODY [47,48]. These included (i) age of onset; (ii) family history of diabetes in three consecutive generations; (iii) absence of insulin resistance and obesity; (iv) negative auto-antibodies; and (v) C-peptide levels. Early establishment of the molecular diagnosis facilitated individual treatment selection for individuals with MODY, to optimize blood glucose levels and prevent long-term complications. Around 14 different genetic mutations are implicated in the aetiology of MODY, with each differing in clinical presentation, extra-pancreatic features, risk of complications, and response to treatment [49]. The commonest types of MODY are the transcription factor linked (HNF1A, HNF4A, and HNF1B-MODY) and the enzyme linked (GCK-MODY).

In terms of prognosis, the risk of developing micro- and macrovascular complications is similar between individuals with MODY-HNF, type 1 diabetes, and type 2 diabetes. The rate of developing such complications is closely related to the individual's overall glycaemic levels [5, 50]. The prognosis for individuals with MODY is to some extent dependent on the underlying genotype. For example, individuals with GCK-MODY have a lower risk for developing vascular or other diabetes-related complications compared to people with type 1 diabetes or type 2 diabetes. The lower risk of complications in these individuals is attributed to the preserved insulin secretion and the non-progressive nature of the disease [51].

With regard to treatment, sulfonylurea derivatives are often prescribed in people with MODY. Those with HNF1A and HNF4A mutations respond well to low-dose sulfonylurea derivatives. DPP-4 inhibitors and GLP-1 RA can be further added to optimize glycaemic levels [48]. In contrast, individuals with the HNF1B mutation require insulin therapy, since they respond minimally or not at all to oral anti-diabetes agents [52]. Individuals with GCK-MODY in general require no treatment and do not respond to either oral anti-diabetes agents or insulin therapy [53].

Precision medicine in type 1 diabetes and type 2 diabetes

The two commonest forms of diabetes are traditionally classified as type 1 diabetes and type 2 diabetes. The diagnosis of type 1 diabetes or type 2 diabetes is based on the presence (type 1 diabetes) or absence (type 2 diabetes) of antibodies against pancreatic islet β-cell antigens, insulin secretion assessed by C-peptide measurement and age (onset of type 1 diabetes generally occurs at a younger age). Approximately 80% of all people with diabetes have type 2 diabetes. However, type 2 diabetes is a heterogeneous disease. A refined classification of diabetes has been proposed, which identifies at diagnosis the individuals at greatest risk of complications who will need intensified treatment. In this new classification, diabetes is stratified into five subtypes with different rates of complications and response to treatment [54]. However, this approach is not routinely used in clinical practice, where the classification of diabetes still relies on the traditional antibody tests and age of onset.

Oral anti-diabetes drugs

The management of individuals with type 1 diabetes and type 2 diabetes encompasses several interventions such as education on physical activity, diet, reduction of cardiovascular risk factors (e.g. smoking cessation, blood pressure control), and the attempt to achieve near normoglycaemia. Early identification and appropriate treatment of the individual are important to minimize the risk of long-term complications. Insulin was discovered in 1921 and since its discovery many other orally available anti-diabetes drugs have been developed. Metformin and sulfonylureas were the first orally available drugs. Metformin remains the first-choice agent in most people with type 2 diabetes. When metformin cannot be prescribed because of contra-indications or side effects, the most recent guidelines recommend SGLT-2 inhibitors and GLP-1 RAs as alternative options, in particular when other comorbidities are present such as cardiovascular disease, chronic kidney disease, or heart failure. Other glucose-lowering agents such as sulfonylurea derivatives or DPP-4 inhibitors can be added as necessary.

There is considerable variation in individual response to all oral drugs in persons with diabetes, which is most likely explained by the marked underlying heterogeneity of the disease. In addition, several other contributing factors are involved, such as medication taking and social and educational status. Multiple studies have been conducted to improve the stratification of people with diabetes and identify subgroups who respond particularly well to a specific drug class. Here we summarize these findings and review the main therapeutic drug classes used in the management of type 2 diabetes.

Metformin

Clinical practice guidelines recommend metformin as the first-line treatment for hyperglycaemia because of its long safety record and broad clinical experience. Metformin principally acts by reducing the synthesis of glucose in the liver through inhibition of gluconeogenesis. Furthermore, it stimulates insulin-mediated glucose utilization in peripheral tissues and decreases food intake, leading to body weight loss. However, metformin is contraindicated in several conditions due to the risk of lactic acidosis, including severe kidney dysfunction (estimated glomerular filtration rate [eGFR] below 30 ml/min/1.73 m^2), active liver disease, and conditions associated with hypo-perfusion of various organs, such as heart failure and sepsis.

The response to metformin varies among individuals, with older age and lower body mass index (BMI) being associated with a larger HbA_{1c} reduction following initiation of metformin [27, 55, 56]. Interestingly, the likelihood of a more favourable response to metformin increases if the drug is started earlier in the course of diabetes, which highlights the importance of early identification of individuals at risk of developing diabetes or in the early stages of diabetes [55, 56].

In addition to clinical and laboratory predictors, several genetic determinants of the pharmacokinetic and pharmacodynamic response to metformin have been described. Genetic variants in the *SLC22A1* gene, encoding the organic cation transporter-1 (OCT-1), and the *SLC47A1* gene, encoding multidrug and toxin extrusion 1 transporter (MATE-1), influence the pharmacokinetic properties of metformin, such as the oral absorption, hepatic uptake, and renal excretion (Figure 30.2). OCT-1 is an organic cation transporter expressed in the brush border of intestinal cells and in basolateral membranes of liver and kidney cells, and has an important role in metformin absorption as well as hepatic and renal secretion of metformin. MATE-1 is a transporter expressed in the luminal membranes of renal proximal tubules and bile canalicular membranes of hepatocytes, which mediates the efflux of metformin and other substrates. Variations in genes encoding these transporters have been associated with differences in the pharmacodynamic response to metformin treatment. The variant rs622342 (AA) in the *SLC22A1* gene, encoding OCT-1, predicted a greater HbA_{1c} reduction in response to metformin compared to individuals carrying the minor C allele [57]. This finding was explained by reduced OCT-1 activity in individuals with C alleles in whom metformin transport across the hepatocyte membrane is decreased. Other OCT-1 genetic variants such as R61C, G410S, 420del, and G465R predicted a lesser response to metformin [58]. A single-nucleotide polymorphism (SNP) in rs2289669 of MATE-1 was associated with a larger HbA_{1c} reduction [57]. This is likely explained by reduced action of MATE-1 transporters, resulting in a reduced efflux of metformin

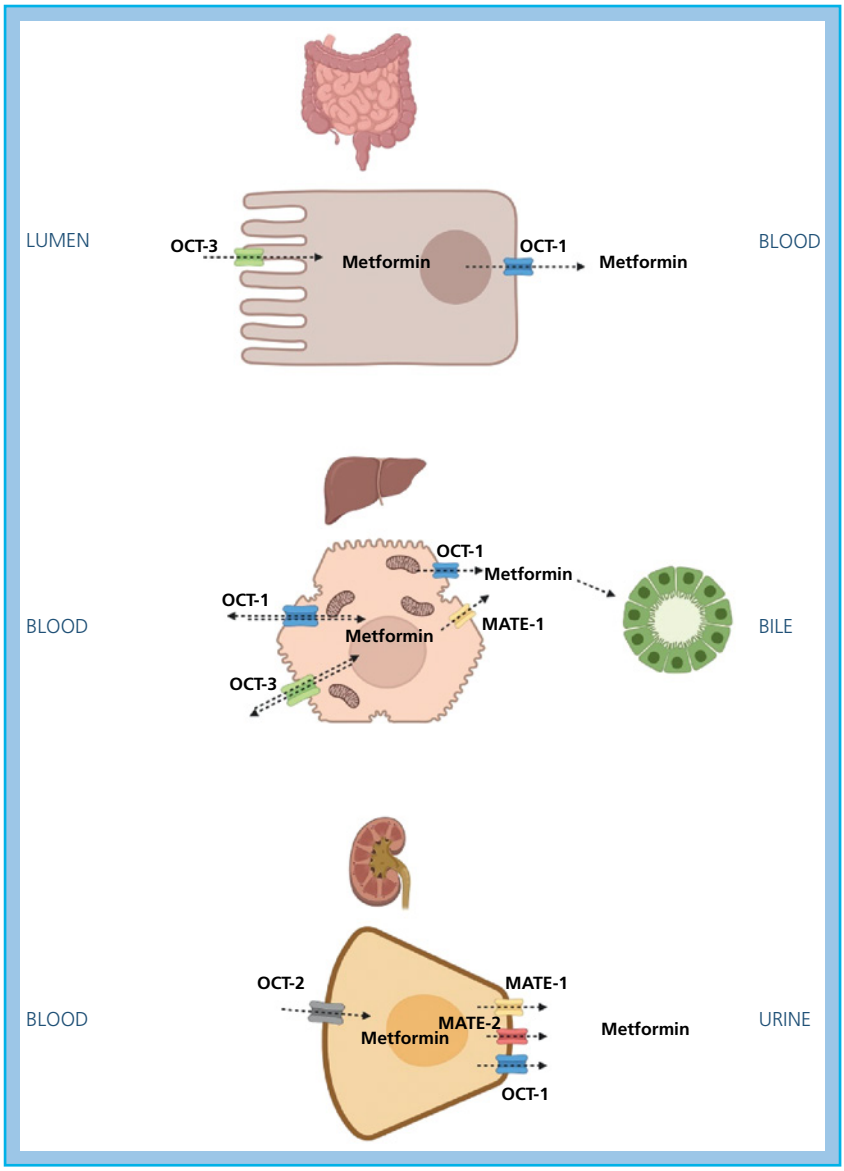

Figure 30.2 Metformin is absorbed from the intestine into enterocytes by several transporters, including organic cation transporter (OCT)-3. OCT-1, which is mainly located on the basolateral side of the enterocytes, enables the transfer of metformin from the enterocytes into the blood. Metformin is absorbed from the bloodstream into hepatocytes by OCT-1 and OCT-3. Multidrug and toxin extrusion (MATE)-1 is present in bile canalicular membranes of hepatocytes and mediates the excretion of metformin with the bile. OCT-2, which is expressed by the basolateral membranes of kidney tubules, is engaged in the uptake of metformin from the bloodstream into the tubular cells. MATE-1, MATE-2, and OCT-1 are responsible for the secretion of metformin from the tubular cells (apical side) into the urine. Genetic polymorphisms in these transporter can alter the disposition of metformin.

from the renal brush borders and from hepatocytes, leading to increased levels of plasma metformin and a stronger inhibition of gluconeogenesis in the liver, with overall a reduction in blood glucose levels.

There are other genetic polymorphisms that may explain the variability in response to metformin. The minor allele (C) of rs11212617 in the ataxia telangiectasia mutated (ATM) locus is associated with a better response to metformin. ATM influences the effect of metformin on 5′ adenosine monophosphate-activated protein kinase (AMPK) and is involved in insulin signalling and pancreatic β-cell dysfunction [59]. In particular, ATM activates AMPK via the phosphorylation of the AMPK α-subunit and it regulates the mitochondrial biogenesis via AMPK [60]. ATM is required for a complete response to metformin [61]. The *SLC2A2* gene encodes GLUT2, a transmembrane protein, which is involved in glucose transport. Genetic variations in GLUT2 have been associated with increased risk for hyperglycaemia and severity of type 2 diabetes symptoms [62]. Individuals with the C allele (rs8192675 variant) of the GLUT2 gene showed a larger HbA_{1c} reduction in response to metformin. The most likely reason is that individuals with this genetic variant have decreased GLUT2 activity in the liver. Hence, glucose has less ability to enter hepatic cells, leading to a reduction in glucose clearance.

Gastrointestinal side effects are observed in ~20–40% of individuals following metformin initiation [63]. The likelihood of developing these side effects is partly determined by genetic polymorphisms. For example, genetic variants of the *SLC22A1* gene were implicated in the occurrence of side effects. Alterations in

metformin transport via OCT-1 led to increased metformin concentrations in the gut, which are in turn responsible for alteration of the intestinal microbiome and intestinal serotonin concentration. Variants of OCT-1 with reduced function are also directly associated with increased systemic concentration of metformin, with consequent metformin intolerance [64]. In addition, drugs that inhibit OCT-1 such as verapamil and proton pump inhibitors are also associated with the severity of gastrointestinal side effects from metformin [58, 65, 66].

Taken together, these genetic findings explain in part the large variation in metformin response with respect to its efficacy and safety. However, the implementation of these findings in routine diabetes care is lagging behind. Most studies have lacked independent validation, which is essential for implementation. In addition, for many physicians it is unclear how these research findings can be implemented in their daily practice. Developing algorithms that can be used easily in clinical practice could be one approach to improve implementation of these findings in daily clinical care.

Sulfonylurea derivatives

Sulfonylurea derivatives act by stimulating the release of insulin from pancreatic β cells, thus determining lower blood glucose concentrations. They inhibit the K_{ATP} channels on pancreatic β cells, leading to cell membrane depolarization and consequently calcium influx and stimulation of insulin secretion [56]. Although sulfonylurea derivatives are effective in lowering blood glucose levels, they may cause weight gain and hypoglycaemia as adverse events. Hypoglycaemia occurs more frequently in individuals with impaired kidney function (eGFR <60 ml/min/1.73 m^2), for whom short-acting sulfonylurea derivatives (e.g. gliclazide, glipizide) are preferred. Several predictors of response to sulfonylurea derivatives have been discovered. Men respond better to sulfonylurea derivatives, and this is probably due to the different activity of cytochrome P450 between men and women [56, 67]. Sulfonylurea derivatives are metabolized by the liver, with *CYP2C9* being crucial in this function [68]. Some sulfonylurea derivatives have active metabolites that are excreted with urine [27, 56, 69, 70]. A shorter diabetes duration is inversely correlated to the response to sulfonylurea derivatives, indicating that the probability of responding to sulfonylurea derivatives increases if the drug is started early after the diagnosis of diabetes.

Variations in several genes influence the pharmacokinetics and pharmacodynamics of sulfonylurea derivatives. Individuals with variants in *CYP2C9* encoding cytochrome P450 2C9 with reduced enzymatic activity have higher exposure to sulfonylurea derivatives and greater response during the initial phase of treatment [71–73]. These individuals generally require a reduced dose to normalize glycaemic levels [72] and to avoid hypoglycaemia [73].

Regarding the genetic determinants of the pharmacodynamic response to sulfonylurea derivatives, variants of transcription factor 7-like 2 (*TCF7L2*) genes, which are involved in regulation of β-cell function, predict a worse response to sulfonylurea derivatives. In a study of 901 people with type 2 diabetes, those with a homozygotes TT genotype for the SNP rs1225372 are twice as likely to be unable to achieve the HbA_{1c} goal of <7% (53 mmol/mol) within one year of sulfonylurea derivatives initiation [74]. Furthermore, variants in *KCNJ11* and *ABCC8*, both encoding the sulfonylurea derivatives receptor, are associated with an increased glycaemic response to sulfonylurea derivatives in type 2 diabetes [71–73, 75]. The Ser1369Ala variant of the *ABCC8* gene and the rs5210 and E23K variants of the *KCNJ11* gene predict a greater response to sulfonylurea derivatives. Other variants that influence the sulfonylurea derivatives response are across genes *IRS-1* and *NOS1AP*. The Arg^{972} variant of *IRS-1* (insulin receptor substrate-1), which is involved in insulin signalling, predicts failure in response to sulfonylurea derivatives [76]. Individuals with risk alleles in *NOS1AP*, encoding a cytosolic protein that binds to the signalling molecule nNOS, were linked to a low response to the sulfonylurea derivative glibenclamide [77].

Dipeptidyl peptidase-4 inhibitors

DPP-4 inhibitors act by inhibiting the enzyme DPP-4, which deactivates several substrates including glucose-dependent insulinotropic polypeptide (GIP) and GLP-1. They stimulate glucose-dependent insulin release from the pancreatic β cells. The great advantage of these drugs is that they exhibit a low risk of hypoglycaemia. There are several clinical and genetic determinants of response to DPP-4 inhibitor treatment. Markers of insulin resistance such as high BMI, serum triglycerides, C-peptide levels, and homeostatic model assessment (HOMA) index are associated with decreased response to DDP-4 inhibitors, measured as absolute change in HbA_{1c} from baseline to six months after start of treatment. Lipotoxicity has an additional effect in reducing response to DPP-4 inhibitor treatment [78].

The genetics of pharmacokinetic variation have largely not been investigated, mainly because these drugs do not interfere with cytochrome P450 and do not act as inhibitors or inducers of the cytochrome system [79]. DPP-4 inhibitors are mainly excreted via the kidney. Conversely, there are several genetic determinants of pharmacodynamic variation. The rs7202877 variant close to *CTRB1* and *CTRB2*, both encoding the enzyme chymotrypsin, predicts a low response to DPP-4 inhibitors [80]. The SNP rs6923761 in the GLP-1 receptor gene predicts a smaller response to sitagliptin or vildagliptin, whereas individuals with variation in rs3765467 of the same gene respond better to these DPP-4 inhibitors [81–83]. Polymorphisms in genes *KCNQ1* and *KCNJ11*, both encoding potassium channels involved in incretin secretion from endocrine intestinal cells, have been associated with increased response to DPP-4 inhibitors [84, 85]. Similar associations have been found with other genetic variants such as *PRKD1* (encoding a kinase involved in regulation of cell proliferation, differentiation, and apoptosis), *CDKAL1* (encoding cyclin-dependent kinase 5, which is involved in regulation of insulin secretion), interleukin-6 (IL-6), *TCF7L2* (encoding transcription factor 7-like 2, which regulates the pancreatic GLP-1 signal), DPP-4, and PNPLA3 (patatin-like phospholipase 3) [86–88].

Glucagon-like peptide-1 receptor agonists

GLP-1 receptor agonists improve glucose levels via multiple mechanisms, including stimulation of glucose-dependent insulin secretion, suppression of glucagon release, decreased appetite and food intake, and slowed gastric emptying. GLP-1 RA do not cause hypoglycaemia unless they are combined with other therapies that increase the risk of hypoglycaemia, such as sulfonylurea derivatives and insulin. Variations in pharmacodynamic response to GLP-1 RA have been investigated. Polymorphisms in the GLP-1 receptor gene (rs6923761) are associated with a greater weight reduction in response to the GLP-1 RA liraglutide, whereas polymorphism in allele T of rs10305420, a polymorphism that causes an amino acid substitution – from proline to leucine – was associated with less weight loss and less HbA_{1c} reduction in response to exenatide [89, 90].

A variant in the cannabinoid receptor 1 (*CNR1*) gene, rs1049353, which is involved in appetite and body weight regulation, was associated with improvement in insulin resistance in response to liraglutide [89]. The gene *TCF7L2* has a diabetogenic effect by altering insulin secretion in type 2 diabetes; an SNP of *TCF7L2* determines a greater reduction of post-prandial insulin peak in people with type 2 diabetes treated with exenatide [91]. The impact of the *TCF7L2* gene polymorphism on therapy response to sulfonylurea derivatives, GLP-1 RA, or DPP-4 inhibitors is depicted in Figure 30.3. As a final comment, the sortilin-related VPS10 domain containing receptor 1 (*SORCS1*) is involved in insulin secretion in humans. Individuals carrying the genotype SORCS1 rs1416406 GG may benefit more from exenatide, since it is associated with a greater reduction in the proinsulin/insulin ratio, which is a marker of insulin resistance and β-cell dysfunction [96]. Thus, various gene polymorphisms are involved in the metabolic response to GLP-1 RA. Most studies have assessed surrogate markers and the extent to which these polymorphisms determine the effect on clinical outcomes during GLP-1 RA treatment remains to be investigated.

Sodium glucose cotransporter-2 inhibitors

SGLT-2 inhibitors promote the renal excretion of glucose by blocking the proximal tubular glucose reabsorption in the kidney, and therefore lower blood glucose levels in individuals with type 2 diabetes. They also have a natriuretic effect and thus lower blood pressure and body weight [21]. Clinical and demographic predictors of response to SGLT-2 inhibitors have been found and represent potential tools for precision medicine [97]. Individuals with higher eGFR appear to show a larger HbA_{1c} reduction in response to SGLT-2 inhibitors. This is likely explained by the fact that, at a higher eGFR, more glucose is filtered in the glomeruli. In the absence of SGLT-2 inhibitors, the filtered glucose would be reabsorbed. SGLT-2 inhibitors inhibit the glucose reabsorption, leading to a larger glucosuric effect and more pronounced reduction in HbA_{1c}. Whether this has clinical consequences in terms of prevention of clinical outcomes is unlikely, as it appears that the long-term benefit of SGLT-2 inhibitors is unlikely to be mediated by reductions in HbA_{1c}.

Some studies have suggested that men experience a greater response to SGLT-2 inhibitors. This may be attributed to a higher

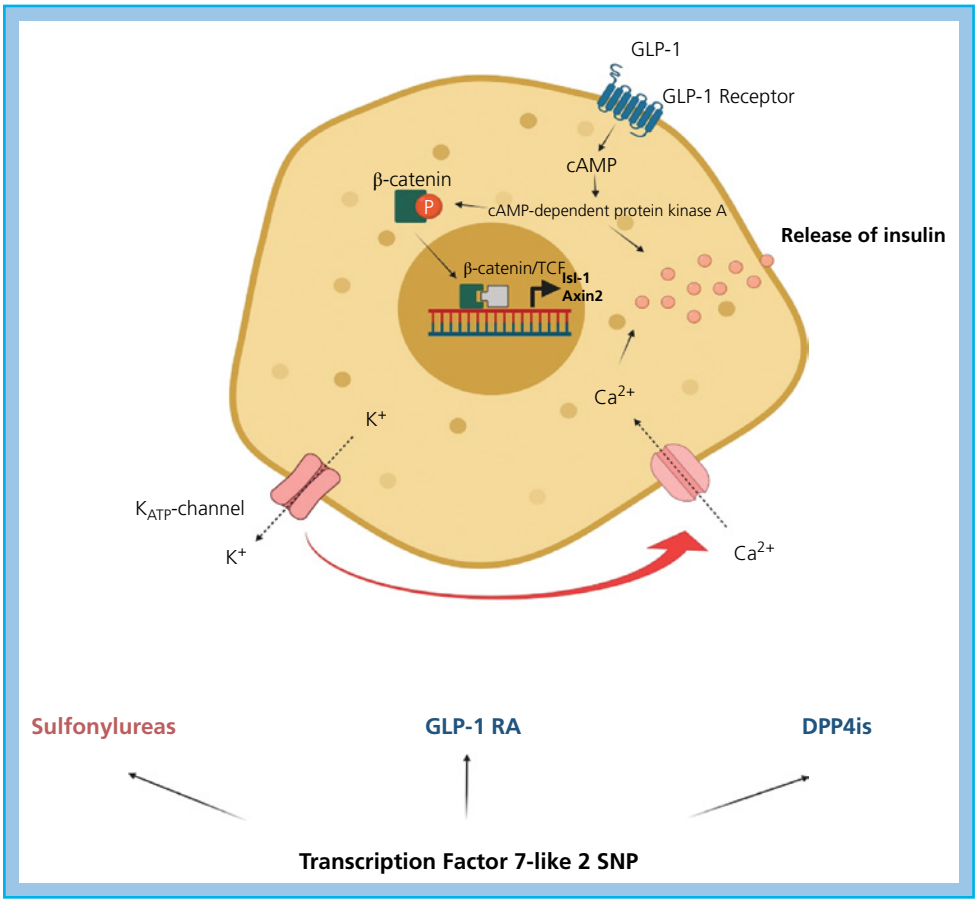

Figure 30.3 Influence of single-nucleotide polymorphisms (SNPs) in the *TCF7L2* gene in response to treatment with sulfonylurea derivatives, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and dipeptidyl-peptidase 4 (DPP-4) inhibitors. In pancreatic β cells, GLP-1 phosphorylates β-catenin via cyclic adenosine monophosphate (cAMP)-dependent protein kinase A (PKA). This abrogates the degradation of the β-catenin that subsequently accumulates, enters the nucleus, and forms the transcription factors β-catenin/TCF. As a result of this mechanism, Wnt/TC expression is enhanced and related genes are activated, including *Isl-1* and *Axin2*. This pathway leads to pro-insulin processing, β-cell protection from interleukin-1β, and interferon-γ mediated apoptosis; stimulates β-cell proliferation; and mediates glucose and GLP-1-stimulated insulin secretion [92–94]. Individuals with *TCF7L2* gene variants (particularly T allele carriers) have altered *TCF7L2* expression in pancreatic β cells, resulting in reduced insulin secretion and impaired response to incretins (GLP-1 RAs, DDP-4 inhibitors) and sulfonylurea derivatives. Whereas impaired response to GLP-1 RAs and DPP-4 inhibitors likely depends on the direct effect of *TCF7L2* on PKA and insulin secretion patterns, the lower response to sulfonylurea derivatives is partially elucidated and seems to be dependent on the general reduction in β-cell insulin secretion and overall β-cell metabolic dysfunction in individuals with these genetic variants [95].

expression of SGLT-2 transporters in men than in women, although this is not consistently observed in all studies [98]. Markers of insulin resistance also predict the response to SGLT-2 inhibitors: proinsulin/insulin ratio and HOMA index are independent predictors of four-week HbA_{1c} reduction in response to SGLT-2 inhibitors, whereas free fatty acid levels predict 24-week HbA_{1c} reduction [97].

Although genetic studies on SGLT-2 inhibitor response are still in progress, both pharmacokinetic and pharmacodynamic variations in SGLT-2 inhibitor response have been reported. Two variants in gene *UGT1A9*, encoding the UGT enzyme, are involved in the metabolism of canagliflozin and other SGLT-2 inhibitors influence their pharmacokinetics. Carriers of the variants UGT1A9*3 and UGT2B4*2 have a higher exposure to canagliflozin and thus a better drug availability [99, 100]. In addition, genetic variants of the *SLC5A2* gene, which encodes the SGLT-2 cotransporter, have been described (Figure 30.4). However, none of the SNPs was significantly associated with response to empagliflozin in terms of change in HbA_{1c}, body weight, or systolic blood pressure [101].

Randomized studies have shown that SGLT-2 inhibitors reduce the risk of cardiovascular and renal outcomes, such as cardiovascular fatal and non-fatal events or end-stage kidney disease [102, 103]. The benefits of SGLT-2 inhibitors in reducing the risk of kidney failure and heart failure are remarkably consistent among individuals and are present irrespective of the degree of kidney impairment, and the presence of heart failure, cardiovascular disease, and even diabetes. This suggests that many people with diabetes would benefit from these drugs and the concept of precision medicine is less relevant. Although this may be true, a clinical trial with dapagliflozin showed that ~20% of treated individuals did not respond to this drug, in terms of systolic blood pressure or albuminuria reduction. Importantly, the same individuals did not respond when they were re-exposed to the same drug (dapagliflozin) at the same dose after a six-week wash-out period [104]. Such an exposure–re-exposure study provides useful information regarding the variability in treatment response, and should be performed for other treatments used for people with diabetes to delineate an individual's drug response and develop strategies to overcome therapy resistance.

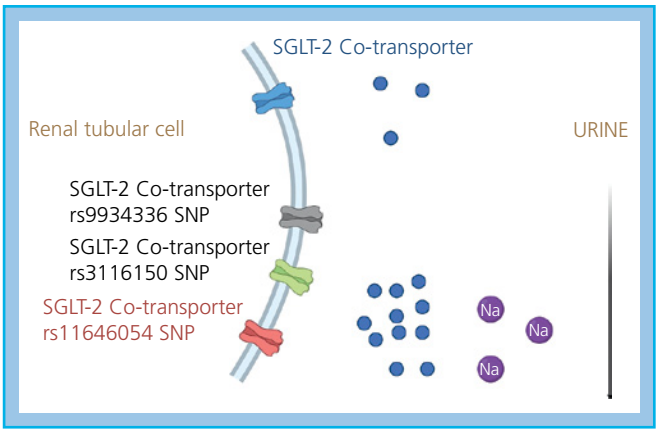

Figure 30.4 The AA genotype rs9934336 in the SGLT-2-encoding gene *SLC5A2* is associated with an SGLT-2-mediated increase in glucose excretion in the urine. Moreover, single-nucleotide polymorphisms (SNPs) rs3116150 and rs11646054 in the *SLC5A2* gene determine a loss of function in SGLT-2 cotransporter with higher excretion of glucose and sodium. This may impact the effect on blood pressure (larger reduction in systolic blood pressure) and glucose control in response to SGLT-2 inhibitor treatment. Studies to test this hypothesis are ongoing.

There is great interest in using these drugs in clinical practice following the results of large clinical trials. However, since not every person benefits maximally or tolerates SGLT-2 inhibitors, and some people experience genital infections or volume depletion, future studies into the underlying pathways of variability in drug response are desired.

Blood pressure–lowering drugs

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

Blood pressure lowering with ACE inhibitors or ARBs is recommended for individuals with type 2 diabetes at high risk of cardiovascular or renal events [105, 106]. The efficacy of ACE inhibitors and ARBs goes beyond their effect on blood pressure. Both drug classes reduce albuminuria, which is an important contributor to the long-term cardiovascular and renal effects [15, 107]. The change in blood pressure and albuminuria varies between individuals and is reproducible on re-exposure to the same drug at the same dose [108] (Figure 30.5). This indicates that the variation in response does not only reflect measurement variation, but is a true variation in pharmacological response. Several determinants may independently or in combination contribute to this response variation. Determinants of therapy response include the type and severity of renal lesions, obesity, insulin resistance, as well as genetic and dietary factors.

The efficacy of ACE inhibitors and ARBs to lower blood pressure and albuminuria is less in individuals with overweight and obesity [110]. The precise underlying mechanisms are not completely understood, but emerging data demonstrate that adipose tissue has endocrine actions [111]. For example, the adipocyte-derived

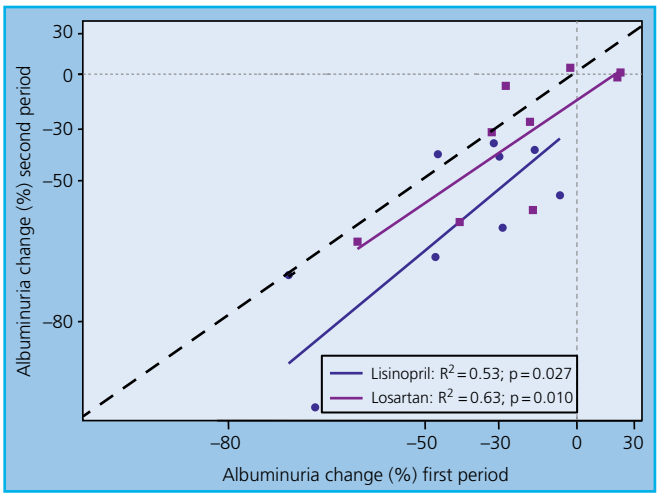

Figure 30.5 Albuminuria response variation to angiotensin-converting enzyme (ACE) inhibitor lisinopril and angiotensin receptor blocker (ARB) losartan during two consecutive exposures separated by a wash-out period. The correlation between the change in albuminuria during exposure and re-exposure to lisinopril and losartan indicates that individuals who did not respond the first time to these drugs also did not respond on re-exposure. This indicates that the variation in response between individuals is not only caused by measurement variation, but also by true drug response variation. Source: Data derived from Petrykiv et al. 2017 [109].

hormone leptin may activate inflammatory mediators such as transforming growth factor (TGF)-β and the renin–angiotensin–aldosterone system (RAAS) and may thereby blunt the efficacy of ACE inhibitors and ARBs.

Another important clinical determinant of therapy resistance to ACE inhibitors and ARBs is sodium status and extracellular volume. Higher volume status is associated with a poor response and interventions that decrease extracellular volume, such as a moderate-sodium diet or diuretic treatment, enhance the blood pressure and albuminuria response to ACE inhibitors and ARBs [112–114]. Moreover, analyses from large clinical trials in people with chronic kidney disease with or without diabetes demonstrated that the efficacy of these drugs to prevent clinically important renal and cardiovascular outcomes was more pronounced in individuals with a lower compared to higher dietary sodium intake [115–117]. These data emphasize the importance of following the World Health Organization (WHO) recommended dietary sodium intake of 5–6 g per day, not only to optimize blood pressure, but also to enhance the efficacy of ACE inhibitors and ARBs (Figure 30.6) [119].

Genetic factors are also involved in the response to ACE inhibitors and ARBs. An insertion (I) or deletion (D) polymorphism of the *ACE* gene modifies the activity of the circulating and renal RAAS, with higher activity in individuals with the deletion polymorphism (Figure 30.7). The blood pressure response to ACE inhibitors is more pronounced in individuals with the DD *ACE* genotype compared to the II genotype, although this finding was not confirmed in all studies. In individuals with chronic kidney disease with or without diabetes, two independent large clinical trials demonstrated that those with the DD genotype were at higher risk of disease progression, but also showed a proportionally larger risk reduction in response to the ACE inhibitor ramipril or ARB losartan [30, 120]. Polymorphisms in the AT-1 receptor gene are also present, but none of these consistently modified the response to an ARB [121].

Lipid-lowering drugs

Hypercholesterolaemia is often observed in people with type 2 diabetes and is an independent risk factor for macrovascular complications [122]. Various drug classes improve lipid profiles and the best known are the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins). Other drugs known to improve lipid profiles are fibrates, ezetimibe, and proprotein convertase subtilisin kexin type (PCSK9) inhibitors, but they are less frequently used than statins [123–125].

Statins significantly reduce low-density lipoprotein (LDL) cholesterol, leading to a reduction in cardiovascular events by 20–50% [126–128]. The benefits of these drugs extend beyond LDL cholesterol lowering alone, with evidence showing broad anti-inflammatory, anti-fibrotic, anti-oxidant, and renal protective effects, which are beneficial to people with diabetes [129–131]. Figure 30.8 shows the detailed molecular mechanism for the effect of statins on cholesterol synthesis, and various pharmacokinetic and pharmacodynamic factors modifying treatment response to lipid-lowering drugs.

HMG-CoA reductase inhibitors – statins

Statins act via competitive inhibition of the rate-limiting enzyme HMG-CoA reductase responsible for cholesterol biosynthesis in the hepatocytes [134]. The present guideline of the American Diabetes Association (ADA) recommends moderate-intensity statin therapy for all individuals with diabetes aged between 40 and 75 years without atherosclerotic cardiovascular disease for primary prevention. High doses of potent statins (atorvastatin or rosuvastatin) are recommended as first-line agents for people with diabetes of all ages to prevent cardiovascular disease [135]. These recommendations were derived from large clinical trials and meta-analyses that demonstrated that every 1 mmol/l (39 mg/dl) reduction in LDL

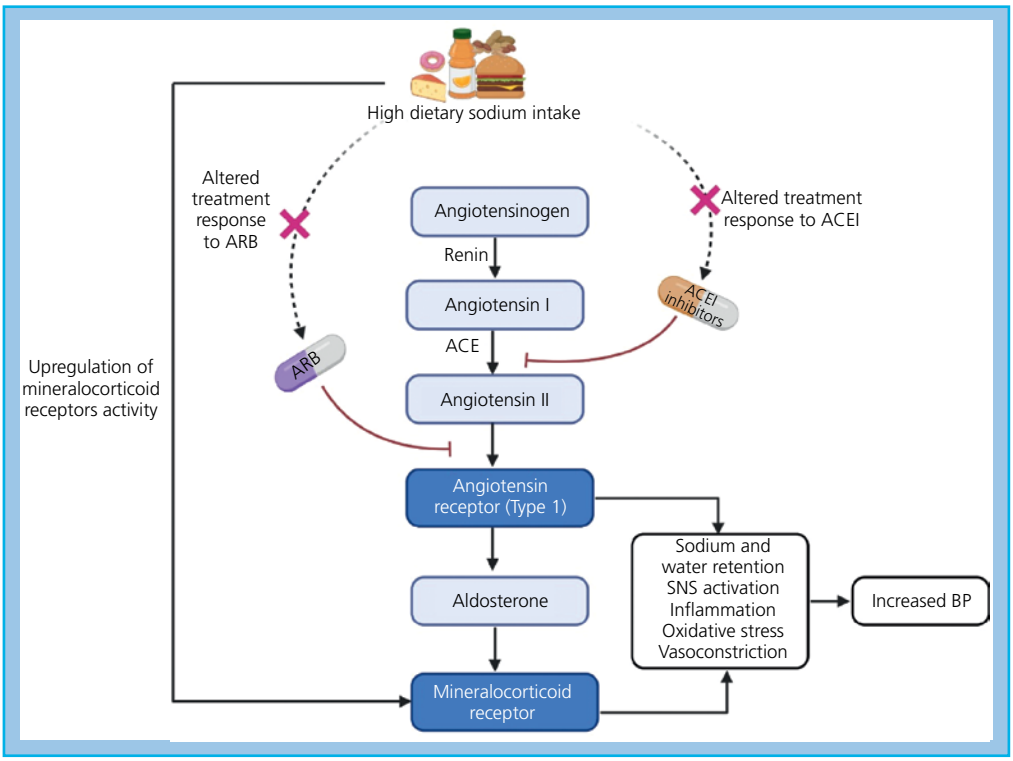

Figure 30.6 The effect of increased sodium intake on the renin–angiotensin–aldosterone-system. Increased dietary sodium could cause direct activation of the mineralocorticoid receptors by enhancing the expression of angiotensin-converting enzymes in the body, leading to a cascade of sodium and water retention, increased inflammation, and sympathetic nervous system activation. In addition, high dietary sodium intake is associated with reduced effect of angiotensin receptor blocker (ARB) in reducing blood pressure and albuminuria among persons with type 2 diabetes, as shown in the *post hoc* analyses of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and the Irbesartan Diabetic Nephropathy Trial (IDNT) trials [118]. ACEi, angiotensin-converting enzyme inhibitors; BP, blood pressure; SNS, sympathetic nervous system.

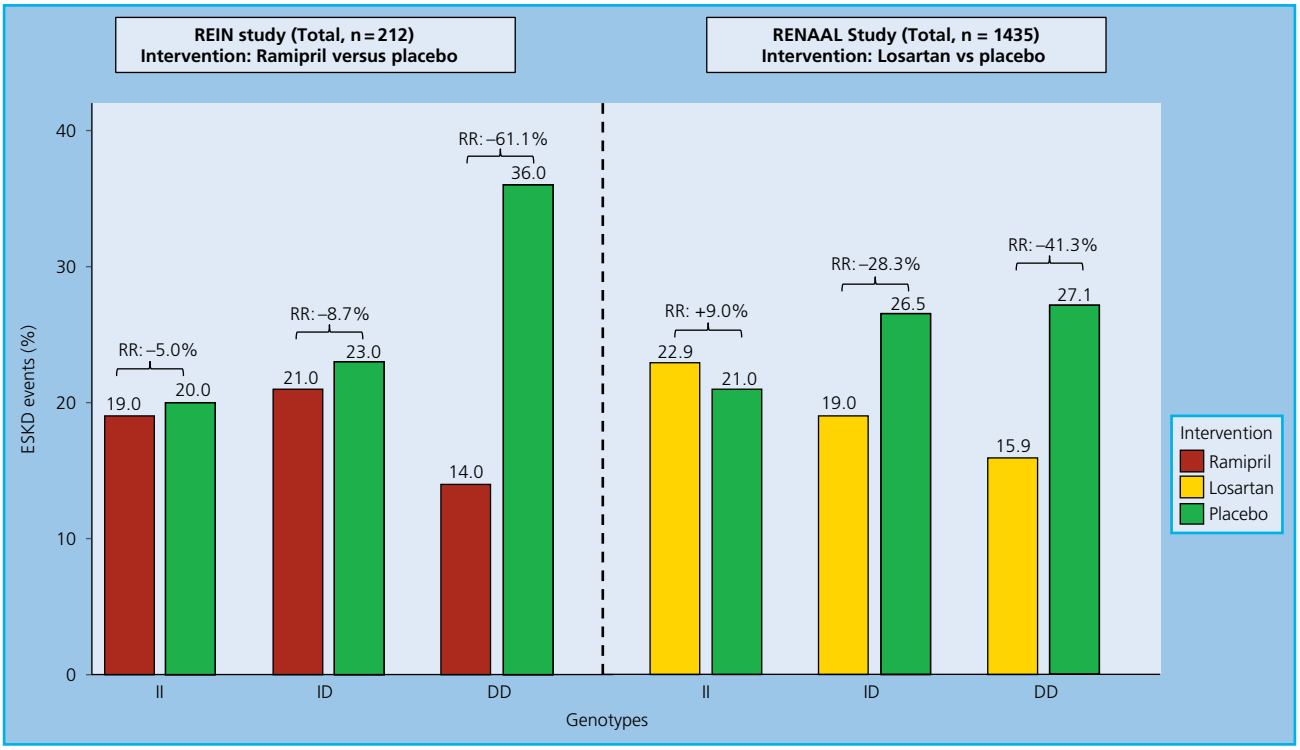

Figure 30.7 In the REIN study (left), individuals with the DD genotype receiving ramipril had a significantly lower number of end-stage kidney disease (ESKD) events (14% vs 36%, p = 0.04), and a relative risk reduction of 61.1%, compared to placebo-treated individuals with the II (5.0%) or ID genotype (8.7%). In the RENAAL study (right), the treatment effect of losartan was greatest among losartan recipients with the DD genotype (a relative risk reduction of 41.3%), compared to individuals with the II (+9.0%) or ID (−28.3%) genotypes for the ESKD endpoint. Source: Data derived from Perna et al. 2016 [30] and Parving et al. 2008 [120].

cholesterol led to a 9% reduction in all-cause mortality and 13% reduction in cardiovascular mortality [16]. In general, statins do not only reduce LDL cholesterol, they also improve high-density lipoprotein (HDL) cholesterol, lower plasma triglyceride, and exert anti-inflammatory effects, which may contribute to their cardiovascular protective effects [136].

The degree of LDL cholesterol lowering varies among individuals. As a consequence, some people do not achieve their target cholesterol level and remain at higher risk for cardiovascular events [137]. Several factors may contribute to the variation in treatment response. Phenotypic factors such as older age, male sex, lower waist circumference, and less alcohol intake were associated with a greater LDL cholesterol reduction following initiation of statins [138–141]. In addition, clinical trials suggested that statins are less efficacious among people who smoke [142]. In the Cholesterol and Pharmacogenetics Study, people who smoke showed significantly less LDL cholesterol and Apo-B reduction (by ~4 mg/dl) in response to simvastatin when compared to non-smokers [138].

SNPs in drug-metabolizing enzymes, such as cytochrome P450, hepatic influx transporters (SLCO1B1), or efflux transporters (ABCB1, ABCC2, ABCG2, and ABCB11), are considered to be major determinants of statin disposition and pharmacokinetic response [143]. Furthermore, lovastatin and simvastatin are lactone pro-drugs requiring *in vivo* activation into β-hydroxy-acid and undergo extensive first-pass hepatic metabolism via CYP3A4 [144]. Individuals with increased CYP3A4 expression have more active metabolites and might derive more pronounced LDL cholesterol reduction with lovastatin, simvastatin, or atorvastatin [145, 146]. Conversely, other statins, such as fluvastatin, are metabolized by CYP2C9, and pravastatin is metabolized via the sulfation process; both are administered as an active hydroxy acid form [147]. Individuals with higher expression of CYP2C9 have better LDL cholesterol reduction when treated with fluvastatin or rosuvastatin due to increased hepatic metabolism [148, 149]. Apart from drug metabolism, transporter proteins are important for the absorption, distribution, and hepatobiliary excretion of statins. Genetic variations in these transporters can also alter statin response. For example, a mutation in the organic anion uptake transporter OATP1B1 results in a lower bioavailability of pravastatin and a reduced LDL cholesterol response [150]. Polymorphism in the *ABCB1* gene decreases drug transport from the intra- to the extracellular compartment. This leads to enhanced intracellular bioavailability of simvastatin and atorvastatin and increased efficacy to inhibit hepatic HMG Co-A synthesis [151, 152].

Polymorphisms in several other genes including apolipoprotein (APO), lipoprotein (a) (LPA), and cholesterol ester transfer protein (CETP) are implicated in the pharmacodynamic response to statins. Mutation of apolipoprotein E impairs the transport of very low-density lipoprotein (VLDL) particles and chylomicrons from the systemic circulation to the liver [153]. As a result, individuals carrying the Apo-E4 allele mutation have more efficient cholesterol clearance from the plasma, thus markedly reduced LDL cholesterol lowering on statin therapy, compared to those carrying Apo-E2 or Apo-E3 [154].

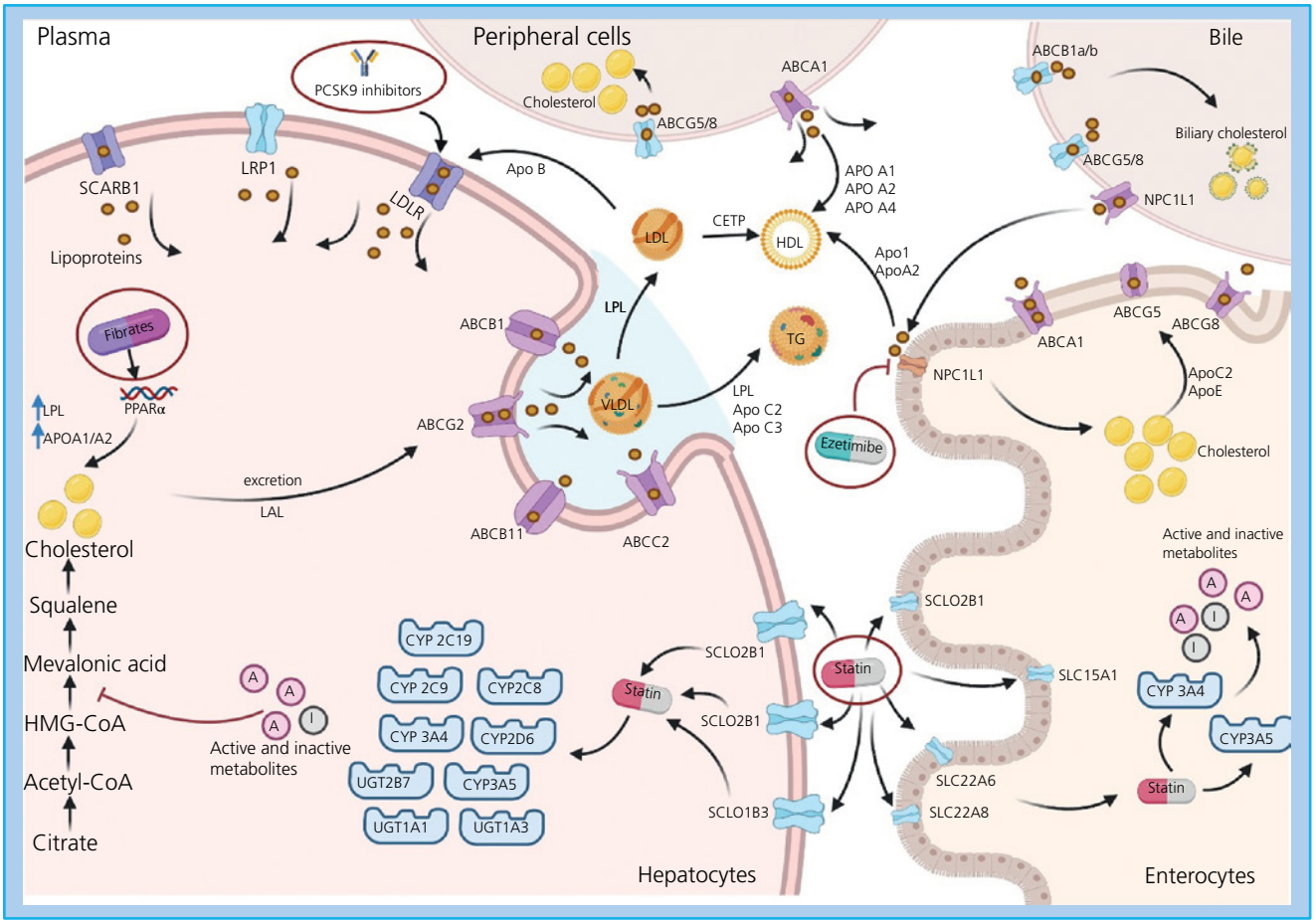

Figure 30.8 Molecular mechanism for the effects of lipid-lowering agents on cholesterol synthesis and the metabolism pathway. Drug transporters on the cell membrane regulate the pharmacokinetics (absorption, distribution, and excretion) of lipid-lowering drugs. Together with the metabolizing enzyme, they modulate the bioavailability and clinical response of the drug. Genetic polymorphism in the cytochrome P450, hepatic influx transporter (*SLCO1B1*), or efflux transporter (*ABCB*) genes thus partly determine the individual response and the degree of lipid lowering with statins. In addition, polymorphism in the genes encoding for lipoprotein receptors, lipid transporters, or enzymatic function can also affect the pharmacodynamic response to these lipid-lowering drugs. For example, polymorphism of the *LDLR* gene leads to familial hypercholesterolaemia and varying response to statin treatment [132]. Polymorphisms in the apolipoprotein-E (*ApoE*) gene affect hepatic clearance of triglyceride-rich lipoprotein on statin treatment. The polymorphism of cholesterol ester transfer protein (*CETP*), particularly the Taq1b variant, modifies the catalytic process between high-density lipoprotein (HDL)-C and triglyceride-rich lipoproteins, and as a result may determine the response to statin therapy [133]. HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; LAL, lysosomal acid lipase; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LPL, lipoprotein lipase; LRP1, low-density lipoprotein receptor-related protein 1; NPC1L1, Niemann-Pick C1-Like 1; PPARα, peroxisome proliferator-activated receptors; SRARB1, scavenger receptor class B (type I); TG, triglycerides; VLDL, very low-density lipoprotein. ABCB1, ABCG2, ABCB11, ABCC2, ABCA1, ABCG5, ABCG8 – human ABC proteins; CYP2C8, CYP2C9, CYP2C19, CYP3A4, CYP3A5, CYP2D6 – cytochrome enzymes; SCLOB1, SCLO2B1, SCLOB3 – SLCO1B1 genotype; SLC22A6, SLC22A8, SLC15A1 – SLC22 genotype; UGT2B7, UGT1A1, UGT1A3 – UDP-glucuronosyltransferases.

Personalized medicine: implementation in clinical practice and future research directions

Clinical and genetic markers can predict the response to many drugs used in the management of diabetes [155–157], but translation of these research findings into clinical practice is slow. This is in part because many studies were not specifically designed to study the variation in drug response and as a consequence their results are considered to be hypothesis generating. In 2021, regulatory guidance recommends only one specific precision medicine approach, namely that genetic testing should be considered for glucose-6-phosphate dehydrogenate deficiency before the use of some sulfonylurea derivatives because of concerns of potential haemolytic anaemia [158]. Nevertheless, clinical practice guidelines have started to make recommendations of drugs for certain subgroups. For example, less stringent HbA_{1c} targets are recommended for older people with diabetes as well as for individuals with severe kidney disease [159], while DPP-4 inhibitors, GLP-1 RA, and SGLT-2 inhibitors are recommended for people with a medical history of recurrent hypoglycaemia. Additionally, individuals with established chronic kidney disease or heart failure should receive SGLT-2 inhibitors and individuals with established cardiovascular disease either a GLP-1 RA or SGLT-2 inhibitor, because of the proven benefits of these drugs on cardiovascular outcomes [22, 23, 160]. Although these are first attempts to tailor glucose-lowering recommendations, further stratification is required to prescribe the right drug for the right individual. All aspects of the disease and treatment response should be considered to further

tailor the medication to the individual. As well as the pathophysiology of the disease, an individual's personality, coping mechanisms, preferences, social network, financial resources, and unique life circumstances should be included, as these factors will also determine when and how a given disease will manifest and how that individual will respond to treatment.

Medication taking is an important aspect, as a poor therapy response often results from suboptimal medication taking. This has been described for many drugs used by people with diabetes and is furthermore not restricted to anti-diabetes drugs. Poorer medication taking is independently associated with a higher risk of diabetes-related complications and increased rates of hospital admission [161, 162]. Understanding why some people do not take medication as prescribed will help improve the delivery of diabetes care, therapy response, and ultimately the prognosis of people with diabetes.

Implementation of precision medicine is challenging without the availability of comparative effectiveness data of various drugs and few insights from the prospective use of genetic and biomarker studies to inform long-term drug efficacy. Ideally, rotation studies or n = 1 studies are performed to compare the efficacy and safety of multiple drugs in a single person [163]. The GRADE study (clinical trial registration NCT01794143) is a head-to-head comparison of four commonly used anti-diabetes agents including a sulfonylurea derivative (glimepride), DPP-4 inhibitor (sitagliptin), GLP-1 RA (liraglutide), and insulin (glargine) among people with type 2 diabetes with less than 10 years of diabetes duration who are receiving standard metformin therapy. The preliminary results of the GRADE study suggest that liraglutide and insulin may result in better glycaemic management than glimepiride and sitagliptin among people with type 2 diabetes in real-world clinical settings. Further analyses will help inform prescribers on which of these agents should be prescribed to each person with diabetes. A couple of other such studies are ongoing: in the MASTERMIND study (clinical trial registration NCT01847144), individuals with type 2 diabetes were randomly assigned to a sulfonylurea derivative (gliclazide 80 mg) or DPP-4 inhibitor (sitagliptin 100 mg) for four weeks followed by a two-week wash-out period, to investigate individual variation in glycaemic response. Finally, the ROTATE trials (clinical trial registration NCT03504566) test in a crossover design how each individual with type 1 diabetes or type 2 diabetes responds to four different kidney-protective drugs: SGLT-2 inhibitors, DPP-4 inhibitors, ARBs, and Janus kinase–signal transducer and activator of transcription (JAK–STAT) inhibitors. These studies will help to address some of the current gaps with respect to variation in response to treatment and the potential impact of the metabolic milieu on the response to glucose-lowering therapies, and may aid in appropriate treatment selection.

Another important initiative is the *All of Us* Research Program. This was started in 2018 and aims to include ~1 million US inhabitants. It is the world's largest longitudinal study conducted so far. The program aims to collect health data (e.g. health-related questionnaires, electronic health record data, physical measurement) and biospecimens (e.g. blood, urine, tissues, DNA, RNA, or proteins) from at least a million people with a diverse background to build a centralized national cohort to study and foster personalized medicine [164]. The ultimate goal of this repository is then to serve as a platform for researchers and healthcare practitioners to advance diagnosis, prognosis, and treatment therapy for the individual, taking into account each individual's lifestyle, environmental, socioeconomic, and biological factors.

Despite the increasing body of evidence that clinical and genetic factors determine the variation in drug responses in monogenic diabetes and type 2 diabetes, translation of basic and clinical science findings to clinical practice is lagging behind. This is partly because of a lack of appropriate independent validation studies and a paucity of implementation studies demonstrating prospectively the benefit of biomarker/genetic-based personalized medicine approaches in reducing long-term clinical outcomes. To implement the research findings in practice, the diabetes community should follow the example from other therapeutic areas such as oncology. A joint commitment from multiple stakeholders including scientists, regulators, physicians, and people with diabetes is necessary to implement personalized medicine approaches to move from a one-size-fits-all to a one-fit-for-each approach.

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6 Treatment of Diabetes

31 Insulin and Insulin Treatment

Roman Vangoitsenhoven[1], Parth Narendran[2], and Chantal Mathieu[1]

[1] Clinical and Experimental Endocrinology, Department of Chronic Diseases and Metabolism, KU Leuven and University Hospitals, Leuven, Belgium

[2] Institute of Biomedical Research, The Medical School, University of Birmingham, and The Queen Elizabeth Hospital, Birmingham, UK

Key points

- Insulin is a peptide hormone essential for life. It is released by the pancreatic β cells in the fasting state to limit catabolism. Post-prandially, insulin secretion is increased to ensure energy storage as carbohydrates, proteins, and lipids, and to stop endogenous glucose production.
- Insulin therapy is necessary in absolute insulin deficiency, as in type 1 diabetes or post-pancreatectomy; however, insulin therapy is also used frequently in states of relative deficiency of endogenous insulin due to insulin resistance, such as type 2 diabetes or gestational diabetes.
- The challenge of insulin replacement therapy is to reproduce a normal physiological insulin profile with low burden to the person with diabetes.
- In 1993, the Diabetes Control and Complications trial showed that intensive insulin therapy can reduce chronic complications of hyperglycaemia, such as retinopathy, nephropathy, neuropathy, and cardiovascular disease, in people with type 1 diabetes. The UK Prospective Diabetes Study demonstrated a reduction of diabetes-related complications through tight glycaemic management in people with type 2 diabetes. However, the risk of hypoglycaemia and insulin-induced weight gain remains a major barrier for treatment intensification.
- Early insulins were extracted from the pancreases of pigs and cows, but optimal glycaemia was difficult to achieve due to impurities in the preparation. Newer and purer insulins, and later synthetic human insulins and insulin analogues, are better tolerated and more predictable in terms of their glucose-lowering effect.
- A range of modern insulin preparations with differing durations of actions are available. These include rapid- and ultra-rapid-acting insulin analogues (duration of action ~2–3 hours), soluble insulin (~6–8 hours), neutral protamine Hagedorn (NPH) insulin (12–18 hours), long-acting insulin analogues (~24 hours), and ultra-long-acting insulin analogues (~40 hours).
- Current recommendations for the injection of insulin are to use the abdomen, upper buttocks, upper arms, and upper thighs, and to rotate injection sites to avoid lipohypertrophy. The needle should be injected at right angles to the skin and left there for 10 seconds before removing the needle. Injection needle lengths should be as short as possible to minimize trauma and to avoid intramuscular delivery. For those using insulin pens, 4 mm needles are available. Syringe needles remain at 8 mm. Alternative routes of insulin delivery such as continuous subcutaneous insulin infusion can also be highly effective.
- Multiple-dose insulin (MDI) therapy is an appropriate initial approach to reproduce the physiological insulin profile in people with absolute insulin deficiency such as those with type 1 diabetes. This comprises a long-acting insulin preparation administered usually once a day to meet the basal insulin requirement, with the injection of a short-acting insulin preparation with each meal.
- Novel technologies, such as insulin pumps that administer rapid-acting insulin continuously through a subcutaneous catheter, provide more flexibility for people with type 1 diabetes. Sensor-augmented smart pump therapy, with automated delivery adapted by an algorithm, reduces the combined rate of severe and moderate hypoglycaemia in people with type 1 diabetes.
- Different insulin injection regimens are available for people with varying degrees of residual endogenous insulin production and insulin resistance, including those with type 2 diabetes, who may already be treated with non-insulin-based therapies. These include a once-daily injection of a long-acting insulin, twice-daily injections of insulin mixtures, or a combination of mealtime short-acting and once-daily long-acting insulins. In addition, insulin can be administered in a co-formulation with other injectables such as glucagon-like peptide 1 receptor agonists.

Discovery and early days of insulin therapy

Insulin is a potent anabolic hormone, and its absence induces a profound catabolic state that affects fat, carbohydrate, and protein stores. Absolute insulin deficiency, as in type 1 diabetes, will result in death if left untreated. In the pre-insulin era, the most effective therapy appeared to be severe nutritional restriction, perhaps most popularly expounded by Frederick Allen from the Rockefeller Institute in New York [1]. This, however, was a difficult regimen that did not appear to prolong life expectancy significantly, and when death came it was unclear whether it was the result of diabetes or starvation.

The relevance and therapeutic potential of insulin arose from the seminal experiments of Frederick Grant Banting and his student Charles Best, although there had been several previous attempts at

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identifying a pancreatic agent that could regulate blood glucose, most notably by the Romanian physiologist Nicolas Paulescu. With the logistical support of John Macleod and help from biochemist James Collip, Banting and Best succeeded in the isolation and purification of an *internal pancreatic secretion* that could normalize glycaemia in pancreatectomized dogs (Figure 31.1). For this work, Banting and Macleod shared the Nobel Prize in Medicine in 1923. In recognition of the essential contributions of the team members, Banting split his prize money with Best, and Macleod shared his portion with Collip. Banting, Best, and Collip shared the patent for insulin, which they sold to the University of Toronto for one Canadian dollar [2]. This remarkable scientific progress took place 100 years ago, and the first dose of insulin was administered to a person with diabetes on 23 January 1922.

Commercially available insulin was initially extracted from porcine and bovine pancreases. This procedure resulted in insulin with a purity of 80–90%, the contaminants largely being pancreatic polypeptides and glucagon. Though this insulin was effective, its use was often complicated by immune-mediated side effects, in particular lipoatrophy and antibody-mediated insulin resistance [3], both of which could profoundly influence the kinetics of insulin action. It was not until 1980 with the introduction of recombinant DNA technology that human insulin therapy became widely available, with purification achieving 99.5–99.9% insulin purity, thus virtually eliminating problems associated with immune-mediated side effects [4].

Figure 31.1 Charles Best and Frederick Banting on the roof of the medical building at the University of Toronto, Summer 1921.

Both beef- and pork-derived insulin remain available in many countries, but leading insulin manufacturers have phased out animal insulins in favour of modern recombinant human insulins. A meta-analysis of 45 randomized controlled trials involving 2156 participants comparing animal and human insulin did not show a significant difference in achieved glucose levels between these two therapies [5].

Advances in insulin manufacturing involved the manipulation of the insulin molecule, resulting in the design and production of shorter- and longer-acting insulin analogues [6]. Analogue insulins are currently favoured due to the closer mimicry of the physiological insulin profile and reduced risk of hypoglycaemia, although generally they are more expensive than human insulin. While those responsible for healthcare budgets seek persuasive clinical trial data on improved overall glycaemic levels, it is most unlikely that we will ever see direct head-to-head studies that provide incontrovertible data one way or another. Most of the benefits of the insulin analogues lie in the increased flexibility and protection against hypoglycaemia, and although some of the individual benefits appear small, collectively they are likely to have an impact on many people with diabetes [7].

Modern insulin formulations to reproduce physiological insulin delivery

Insulin is a peptide hormone of 51 amino acids that is secreted by the pancreatic β cells within a narrow physiological range. In the fasting state, insulin circulates at a concentration of 15–20 mU/l to limit catabolism. Post-prandially, insulin secretion increases to 60–80 mU/l to ensure energy storage of nutrients as carbohydrates, proteins, and lipids, and to stop endogenous glucose production (Figure 31.2). The secretion and action of insulin are covered in more detail in Chapters 7 and 9, respectively.

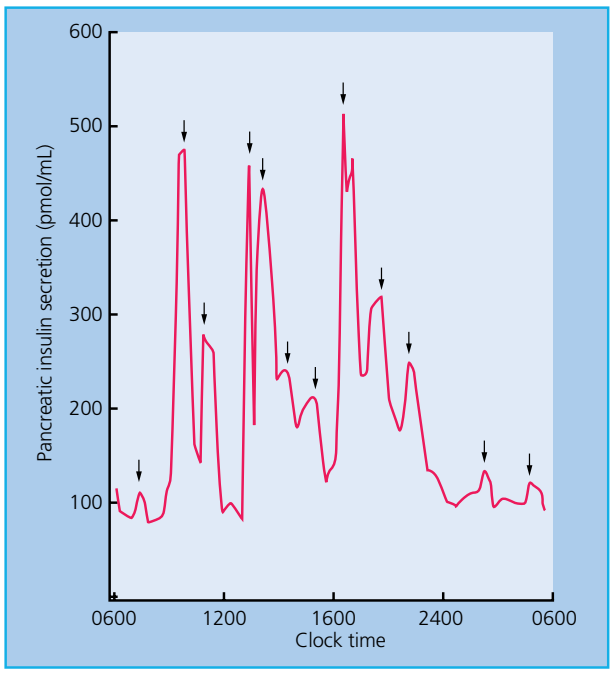

Figure 31.2 Pancreatic insulin secretion in healthy individual with normal body weight. Meals were consumed at 09.00, 13.00, and 18.00. Statistically significant pulses of secretion are shown by the arrows. Source: Polonsky et al. 1988 [8]. Reproduced with permission from the American Society for Clinical Investigation.

Insulin is stored in the β cells as hexamers stabilized by zinc ions (Figure 31.3). When secreted, the zinc-insulin hexamers are diluted in the bloodstream, disassembling into monomers, the active state of insulin. In exogenous insulin administration, hexamer formation can be induced by additives to form stable solutions for vials and cartridges. Classic additives are zinc, a phenolic preservative (m-cresol and/or phenol) that serves a dual purpose as an antibacterial agent and a hexameric stabilizer, and a buffer to maintain the correct pH. Following injection, fluid is drawn into the injected insulin depot through osmosis. This leads to dilution of the insulin and dissociation of the insulin molecules; this is a spontaneous but gradual process that must occur before insulin crosses the capillary walls as monomers into the blood circulation [10]. People with diabetes are therefore advised to inject their soluble insulin 15–20 minutes before a meal to ensure that circulating insulin levels are optimal at the time their meal is being absorbed. A significant proportion of people with diabetes find it hard to follow this advice because of the planning required. Even when they do, the calculated doses may be inaccurate, particularly if the preparation and presentation of the meal are not under the individual's control.

In order to mimic the endogenous insulin response as closely as possible, the time–action profiles of insulins and formulations have been modified over time with the creation of insulin analogues (Figure 31.3). To reproduce the basal and post-prandial insulin secretion, a combination of short-acting and intermediate or long-acting insulin formulations is used [9].

Short-acting formulations

The biological action of soluble human insulin lasts 5–6 hours. The first rapid-acting insulin analogues were designed to form less stable insulin hexamers, ensuring that the insulins would more readily become monomeric, thus moving into the bloodstream more rapidly after subcutaneous injection. These changes result in faster absorption of insulin into the bloodstream and allow it to be injected closer to the mealtime, often just before starting to eat.

One way to reduce the association between insulin molecules is to change the amino acid sequence, usually focusing on the B28–29 amino acids [11]. To date, three such rapid-acting analogues have become available. Insulin lispro (Humalog®, Eli Lilly, Indianapolis, IN, USA) differs from human insulin at position B28 where the amino acid proline is replaced by lysine, and the lysine in position B29 is replaced by proline. Insulin aspart (NovoRapid®, Novo Nordisk, Bagsvaerd, Denmark) also has a substitution at B28, with proline replaced with

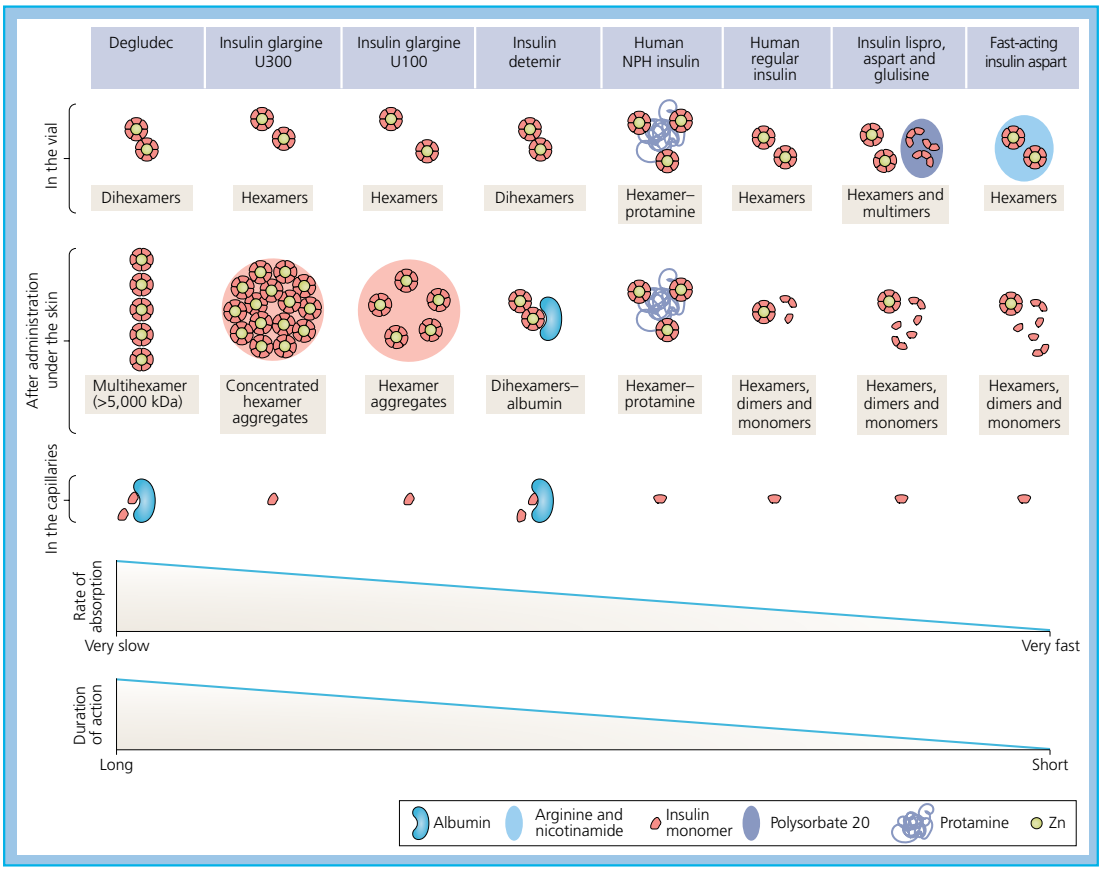

Figure 31.3 Different determinants of absorption and duration of action of human and analogue insulins. Degludec forms weak hexamers in solution in the vial and stable multihexamers after administration at the injection depot, thereby slowing its absorption. Reversible binding to albumin in the circulation further prolongs its action. Insulin glargine U300 precipitates at physiological pH, forming compact aggregates at the injection depot, leading to a reduced surface area from which absorption can occur, causing slow absorption and prolonged duration of action. Insulin glargine U100 also precipitates at physiological pH but is less compact than insulin glargine U300. Insulin detemir forms weak dihexamers in the vial and strong dihexamers at the injection depot. Reversible binding to albumin, both at the injection depot and in circulation, further slows the absorption rate and prolongs the duration of action. Neutral protamine Hagedorn (NPH) insulin co-crystalizes with protamine, both in the pharmaceutical preparation and at the injection site, slowing absorption and action. The classic rapid-acting insulin analogues (lispro, aspart and glulisine) dissociate into dimers and monomers more rapidly than does human regular insulin, causing a more rapid absorption and shorter duration of action. For glulisine, polysorbate 20 is used as a stabilizing agent, and formation of hexamers is prevented by absence of zinc (Zn). More rapid absorption and earlier action of fast-acting insulin aspart is caused by addition of arginine and nicotinamide to the formulation, thereby increasing the rate of formation of monomers at the injection depot and increasing the rate of absorption.

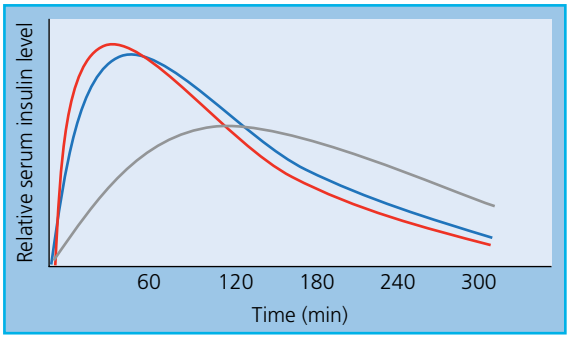

Figure 31.4 Time–action profiles of short-acting insulin formulations. Pharmacokinetic profile of human regular insulin (depicted in grey), rapid-acting insulin analogues (insulin lispro, aspart, glulisine; blue), and ultra-rapid-acting insulin analogues (faster insulin aspart and ultra-rapid lispro; red).

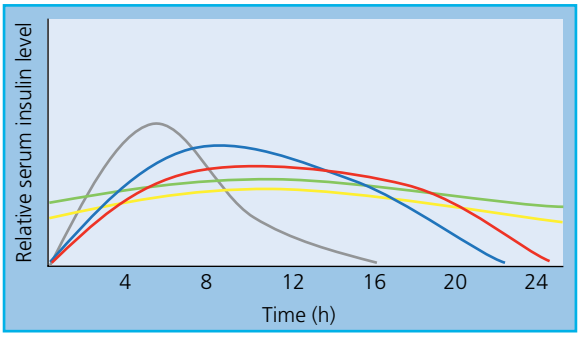

Figure 31.5 Time–action profiles of intermediate and long-acting insulin formulations. Pharmacokinetics profile in steady state of neutral protamine Hagedorn (NPH) insulin (depicted in grey), insulin glargine U100 (red), insulin detemir (blue), insulin glargine U300 (yellow), and insulin degludec (green). Care must be taken when interpreting the curves as the experimental setting in which the data were gathered differed among studies.

aspartic acid. For insulin glulisine (Apidra®, Sanofi, Paris, France), the lysine at position B29 is replaced by glutamic acid, and asparagine at position B3 is replaced by lysine. These analogues act more quickly (within 10–20 min) and have a shorter duration of action (3–5 h) than soluble insulin (30–60 min and 6–8 h, respectively) [12] (Figure 31.4).

Numerous studies have demonstrated the safety of rapid-acting analogues in both type 1 diabetes and type 2 diabetes, as either part of a *basal-bolus* insulin injection regimen combined with intermediate-acting insulins, or in continuous subcutaneous insulin infusion [13]. The time–action profile of rapid-acting analogues is well suited to mimicking the requirement at mealtimes, and therefore they probably control post-prandial hyperglycaemia more effectively than soluble insulin. As a result, individuals can achieve better glycaemic levels and fewer episodes of hypoglycaemia with rapid-acting analogues than with soluble insulin. The benefits of rapid-acting analogues over soluble insulin appear to be clearer in studies involving people with type 1 diabetes than type 2 diabetes, and when using insulin pumps rather than multiple-dose injections [12].

Recently, the addition of excipients to expedite absorption from the subcutaneous space has led to novel formulations of ultra-rapid-acting insulin analogues. Faster insulin aspart (FIASP®, Novo Nordisk) contains L-arginine as a stabilizer and niacinamide to increase absorption by increasing subcutaneous blood flow. Similarly, ultra-rapid lispro (Lyumjev®, Eli Lilly) contains additional citrate to increase absorption by enhancing local vascular permeability and treprostinil to increase local vasodilatation [14]. While both formulations reach peak insulin levels a few minutes earlier, have an earlier offset of action, and achieve a greater reduction in post-prandial glucose compared with rapid-acting insulin analogues, the added value for clinical practice is unproven, and their use in pumps and compatibility with pump catheters need to be studied further.

Intermediate and long-acting formulations

To avoid the frequent painful injections of early insulin preparations, attempts were made in the 1920s and 1930s to provide the daily insulin requirement in just one injection. Modifying agents such as lecithin, oil, and cholesterol were used [15], but the duration of action varied significantly from injection to injection, which limited their clinical utility. In 1936, a method was reported incorporating the addition to insulin of protamine, a highly basic protein derived from the sperm of salmon or trout, to form a poorly soluble complex, thus slowing its absorption [16]. This technique was later refined by adding protamine and zinc in stoichiometric proportions (so that there was no free protamine or zinc) to form isophane or neutral protamine Hagedorn (NPH) insulin. Though the action of NPH insulin is delayed and can cover a 12–24-hour period, significant variation in duration of action and absorption persisted [17]. Consequently, attempts at stringent glucose management using these formulations as basal insulin are associated with an increased risk of hypoglycaemia.

As for rapid-acting analogues, modification of the insulin molecule primary amino acid sequence can also result in a longer and more reproducible duration of action. There are currently three such insulin analogues. Glargine (Lantus®, Sanofi) achieves prolonged insulin action through amino acid substitutions that make the insulin molecule less soluble. Glargine insulin forms microcrystals following subcutaneous injection that dissolve slowly over an 18–26-hour period (Figure 31.5) [18]. In non-inferiority studies, insulin glargine achieves similar glycaemic levels as isophane insulin, but does so with less hypoglycaemia [19]. Insulin detemir (Levemir®, Novo Nordisk) has a fatty acid side chain addition to the insulin molecule that promotes binding to circulating albumin, which then slowly dissociates, giving it a duration of action just a little short of glargine insulin. Detemir is as efficient as isophane insulin at improving glycaemic levels, but again does so with less hypoglycaemia and interestingly less weight gain [20].

The most recent commercially available addition to the long-acting insulin analogues has been insulin degludec (Tresiba®, Novo Nordisk). Degludec also has a fatty acid side chain, but structured in such a way as to encourage it to form long multihexamer chains following subcutaneous injection. This chain disassembles very slowly and gives degludec a very long duration of action (half-life exceeding 25 h), such that it has been termed an ultra-long-acting insulin analogue [21]. This long duration of action allows a very flat insulin profile and a more reproducible duration of action that is not significantly affected by variations in the time of day-to-day administration. Non-inferiority studies have shown that insulin degludec achieves similar glycaemic levels to insulin glargine, but with less overall and nocturnal hypoglycaemia [22].

Comparative studies of the long-acting analogue insulins have been designed to demonstrate equivalence rather than superiority in terms of glycaemia [23]. They do, however, demonstrate that the same level of glycaemia can be achieved with less hypoglycaemia, and some with less weight gain (detemir). These benefits come to date at a cost, with insulin analogues costing more than double the price of NPH insulin.

Biosimilars

Several patent protections for insulin analogue preparations have expired, and the pharmaceutical industry has explored these opportunities to develop *copycat* insulins to compete with original formulations. Because insulins are currently produced biologically (i.e. through expression in living cells), they are more correctly termed *biological* or *biosimilar* drugs than generic drugs. Biosimilars (such as peptide hormones and monoclonal antibodies) are already in clinical practice and are required to undergo more rigorous testing than standard generic drugs. This testing includes direct comparison of the biological activity, pharmacology, clinical safety, and efficacy of the biosimilar with the reference insulin. While the development costs of biosimilars are higher than those for other generic drugs, they are not as expensive as developing the original insulin, and any cost savings will likely be magnified through long-term prescription. Therefore, these insulins will likely be cheaper, thus expanding market competition and increasing availability for people with diabetes. Currently, several biosimilars of insulin have been approved by various regulatory agencies: glargine (Abasaglar®, Eli Lilly) by the European Medicines Agency (EMA; 2014) and US Food and Drug Administration (FDA; 2015); Basalin® (Gan & Lee, Beijing, China) by China (2005); Semglee® (Biocon Biologics/Mylan, Bangalore, India/Canonsburg, PA, USA) by Australia (2018); and insulin lispro (Admelog®, Sanofi) by the FDA (2017) [24].

Concentration

Insulin *units* were introduced to address and compare the blood glucose-lowering potency of insulin preparations. One unit of insulin generally has the potential to drop blood glucose by 50 mg/dl (2.8 mmol/l), although it can range from 30 to 100 mg/dl (1.7–5.6 mmol/l), depending on individual insulin sensitivity. Injecting large volumes of insulin, as is required in those who are insulin resistant, slows absorption kinetics and reduces the effectiveness of the insulin. Furthermore, it can be more painful. Splitting the dose across different injection sites can reduce the volume. However, in some people the use of more concentrated insulin is more appropriate. Insulin preparations are currently standardized to 100 U; that is, 100 units of biological activity per ml of insulin. Concentrating human insulin, however, typically leads to a protraction of its action [25] and ultra-concentrated human insulin (for example, human regular insulin U500) has a pharmacokinetic profile that is intermediate between U100 and NPH [26].

Concentrated formulations of analogue insulins are available for clinical use and have been demonstrated to be clinically effective [27–29]. While the U100 and U200 formulations of short-acting lispro and long-acting degludec have bioequivalence, for one insulin analogue hyperconcentration from U100 to U300 has led to the 'creation' of a new commercial entity (U300 glargine, Toujeo®, Sanofi). U300 glargine has a protracted action exceeding that of U100 glargine, with a duration of action of 25 hours. In clinical trials comparing U100 and U300 glargine, similar glycaemic levels were demonstrated, with a reduced risk of (nocturnal) hypoglycaemia in those using the U300 formulation.

Insulin administration

The early experiments of Frederick Banting quickly revealed that the oral route of insulin administration was not an effective means of insulin delivery, as the insulin molecule is functionally degraded by gut peptides. Subcutaneous injection of insulin has become the most popular route of insulin delivery, because of its relatively reproducible kinetics of absorption and the ease with which it can be administered, but it is worth considering some of the other routes.

Subcutaneous insulin injections

Subcutaneous insulin injections are the most used insulin therapy. The recommended sites for injection are the abdomen, upper arms below the deltoid region, upper thighs, and upper buttocks (Figure 31.6). The area should be clean and free from signs of infection or lipohypertrophy.

Insulin can be directly dialled up on a pen device or drawn up using a disposable syringe. If the insulin preparation is cloudy (e.g. NPH), it should be gently rolled and inverted 10 times. This will allow the insulin crystals to disperse and for the mixture to turn to a milky-white suspension. If using a pen device for insulin delivery, the device should be properly primed and a drop of insulin should be visible at the tip of the needle. Similarly, if an insulin syringe is being used, the barrel should be tapped and any air excluded by squeezing the plunger. These manoeuvres ensure that air is not contributing to the volume of insulin that has been dialled or drawn, and that an accurate dose of insulin is delivered.

The needle should enter the skin at right angles to the surface in a smooth process, the plunger squeezed gradually and completely, and left there for 10 seconds to allow the insulin to enter the tissue.

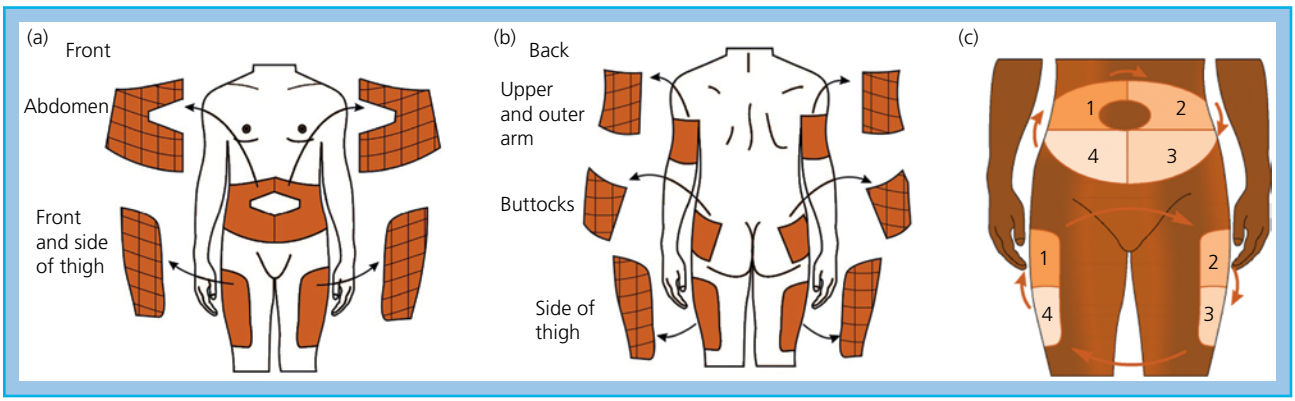

Figure 31.6 Insulin injection sites and rotation of insulin injection sites. The areas recommended for insulin injections as viewed from the front (a) and back (b). They may be divided up into smaller areas, so that each area is injected not more than once a day. (c) A method that can be adopted to rotate insulin injections. Source: Adapted from Bahendeka et al. 2019 [30].

Disposable syringes should be replaced at each injection; for pens it is considered good practice to change the needle for every injection, but this should be done at least once daily. Rubbing of the skin following injection is discouraged because this increases the rate of insulin absorption and may increase the risk of hypoglycaemia.

Syringe needle lengths are currently restricted to 8 mm. Pen needles come in a variety of lengths, including 4, 5, 6, and 8 mm. There is no indication to use needles longer than 8 mm because longer needles increase the risk of intra-muscular injection, with the associated rapid absorption and risk of hypoglycaemia. Currently 4 mm needles are recommended for many adults and most children, and these can often be used without the need to lift skin folds. Injecting into lifted skin folds is appropriate in children, slim adults, and when there is a risk of injecting into muscle. The correct technique for lifting skin folds needs to be taught; it should not lift up underlying muscle, nor be so tight as to cause blanching of the skin (Figure 31.7). The use of lifted skin folds is recommended for all people who use 8 mm needles. Injecting through clothing is discouraged because as needle lengths get shorter, there is a risk of intradermal injection.

Studies of absorption of subcutaneously administered insulin have used various techniques, including measuring the rate of loss of I^{125}-labeled insulin from the site of injection using a gamma counter [32]. They show that the rate can vary significantly between individuals, but also from one injection to another within the same individual [17]. Absorption rates in individuals with obesity are slower than in people without obesity, and there do not appear to be any clear differences in the rate of absorption between the different injection sites. In lean individuals, the absorption of insulin analogues (both rapid- and long-acting) does not appear to vary by injection site [33,34]. However, in these individuals absorption of human insulin from the abdomen appears to be faster than from the arm or leg [35], and the upper abdomen faster than the lower abdomen [36]. This difference can be utilized to good effect, for example injecting NPH insulin into the thigh or buttock ensures slower absorption, and soluble mealtime insulin in the abdomen more rapid absorption.

Repeated injection of insulin at the same site leads to local hypertrophy of adipose tissue, resulting in slower and more erratic insulin absorption. People with diabetes should always be advised to rotate their insulin injection sites to avoid this complication and should be shown an easy-to-follow rotation scheme (Figure 31.6). Other local factors such as oedema or local inflammation can influence rates of absorption. Exercise results in greater blood flow to the skin and can lead to faster uptake of insulin, particularly when that is injected into an area close to the muscle groups being exercised. Individuals who are planning to run, for example, should be advised that injection into the leg may be less favourable than injecting into the arm or abdomen [37]. Similarly, temperature influences cutaneous blood flow and can affect insulin absorption [38]. Hot climates or sitting in the sauna may result in a rapid surge in insulin levels, whereas the converse, travelling to cooler climates, can result in a slower uptake. There are also reports that hypoglycaemia and smoking can reduce the rate of insulin absorption [39,40].

Standard insulin preparations have a shelf life of 4–6 weeks when stored at under 25 °C. Storage for longer periods will require that they be kept in a fridge (4 °C), which then allows them to be stored until their expiry date. Exposure of insulin to high temperatures or to microwaves can render it inactive.

Continuous subcutaneous insulin infusion

Next to delivery by pen or disposable syringes, insulin can be administered to the subcutaneous space using a pump device, which is discussed in detail in Chapter 33.

Alternative routes of insulin administration

Intramuscular injection is more painful, and absorption more rapid, than subcutaneous injection and is not recommended for any insulin formulation [41]. However, this route can be useful in the emergency situation when intravenous access is difficult. Inadvertent intramuscular administration should be considered in lean individuals who complain of pain on insulin injection, and who may experience erratic glucose levels and hypoglycaemia. The correct choice of insulin needles can help address this problem.

The delivery of insulin directly into the peritoneal space, for example, with implantable pumps or directly via a port [42] mimics physiological insulin secretion, in that insulin bypasses the systemic circulation and directly enters the portal circulation. The theoretical advantages of portal delivery include rapid insulin absorption, near physiological carbohydrate and lipid metabolism, and avoiding peripheral hyperinsulinaemia [43]. The clinical advantages of intraperitoneal insulin delivery have been explored in a number of clinical trials [44]. While some evidence exists for improved glycated haemoglobin (HbA_{1c}) and quality of life in selected people with type 1 diabetes [45], the use of this delivery method is limited. However, research is ongoing and the role of implantable pumps in the development of a true artificial β cell remains appealing.

Insulin administration via the respiratory mucosal surface avoids degradation by gut peptides and can be an effective route for insulin delivery, particularly for those who have needle phobia [46]. Inhaled insulin was made available in Europe (Exubera®, Pfizer, New York, USA) in 2006, but was withdrawn within a year due to poor uptake

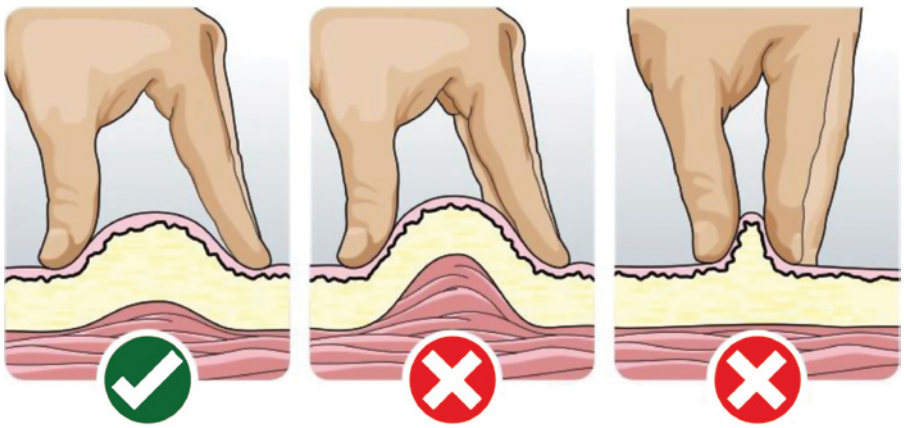

Figure 31.7 The recommended technique for lifting skin folds for subcutaneous injection of insulin. Source: FIT UK Forum for Injection Technique 2016 [31]. Reproduced with kind permission of BD Medical Diabetes Care.

by people with diabetes and healthcare professionals. In 2015, Technosphere insulin, a dry-powder formulation of human regular insulin adsorbed onto microparticles that are inhaled, was approved in the USA for use as a mealtime rapid-acting insulin (Afrezza®, MannKind, Westlake Village, CA, USA). With both formulations, there is a reduction in lung function that reverses when the therapy is stopped, and there is the potential risk of lung cancer in heavy smokers. Afrezza is not recommended in people who are current smokers, or in those with reactive airway diseases such as asthma or chronic obstructive pulmonary disease. While trials of newer inhaled insulins are awaited, systematic reviews of previous formulations suggest they are as clinically effective, but not as cost-effective, as short-acting injectable insulin in unselected people with diabetes [47].

Complications of subcutaneous insulin therapy

The major and most feared complication of insulin injections, which affects most people using insulin, is hypoglycaemia. The causes, avoidance, consequences, and management of hypoglycaemia are discussed in Chapter 40. The fear of hypoglycaemia may be a major barrier to insulin initiation and intensification.

Insulin not only restores fat and muscle mass in newly or suboptimally treated people requiring insulin, but can lead to excessive weight gain [48]. This remains a major concern for many people, particularly those with type 2 diabetes who already have overweight and can no longer be managed with oral anti-diabetes agents. Weight gain is also becoming a growing issue for people with type 1 diabetes, limiting the appeal of intensive insulin therapy [49]. Weight gain can be reduced by concomitant dietary advice and an insulin regimen tailored to the requirement of the individual, which wherever possible provides most insulin when needed; that is, at mealtimes. Overaggressive insulin titration regimens leading to low blood glucose and stimulation in appetite can lead to excessive weight gain. The management of diabetes for some people, particularly but not exclusively young women, can be challenging when insulin doses are reduced to suboptimal levels to manipulate body weight (Chapter 65).

Immune responses to the older animal insulins have been well reported, but such responses to current human and analogue insulins are less common [50]. Allergies may rarely develop in response to the insulin molecule (this may become a more common issue with the introduction of biosimilar insulins where folding may differ) or to components of the insulin preparation (such as protamine or metacresol). Most commonly, allergic reactions manifest as local acute urticarial reactions. These are best managed with intradermal skin testing of 1 : 20 dilutions of different insulin preparations, and then switching to that which is best tolerated [51]. Antihistamines may be of benefit, as too may high-dose steroids in exceptional circumstances. More rarely, widespread systemic reactions develop as a reaction to the insulin and these individuals may benefit from referral to clinical immunology services.

Local complications of insulin therapy include lipoatrophy and lipohypertrophy. Lipoatrophy, in which subcutaneous tissue at the site of injection disappears or atrophies, is an allergic response predominantly with the older animal insulins and is rarely seen today. In contrast, lipohypertrophy occurs commonly. It is not an allergic response, but develops because of a trophic response of adipose tissue to insulin. It is most commonly seen in those with a poor injection technique and usually in people who do not rotate their insulin injection sites. Sustained injections into sites of hypertrophy can lead to poor and delayed insulin absorption, with consequent effects on blood glucose levels [52]. Lipohypertrophy generally resolves within two months if injecting into the affected area is avoided. Occasionally mild ulceration, pitting, and, more commonly, bruising can occur at injection sites. Rotating injection to another site and selecting a shorter needle may be indicated.

Importance of education and assessment of glycaemia

Diabetes self-management education and support is a central component of diabetes therapy for all those living with diabetes [53]. Education should target lifestyle and complication prevention, but in the case of those treated with insulin, glucose monitoring, adaptation of insulin doses, overall nutritional advice, and specifically carbohydrate assessment and glucose monitoring should be central (Chapter 26) (Figure 31.8).

Figure 31.8 A pictorial representation of the standards for diabetes self-management and structured education programmes for people with type 2 diabetes (in the UK). Source: Adapted from Hadjiconstantinou et al. 2021 [53].

While national and international guidelines have made recommendations on glycaemic targets based predominantly on HbA_{1c} [54], self-monitoring of blood glucose not only helps people with diabetes achieve HbA_{1c} targets by adjustment of insulin doses, but also helps them better understand their own diabetes and blood glucose levels (Chapters 29 and 32).

People with insulin-dependent forms of diabetes, including type 1 diabetes and pancreatic forms, who are treated with intensive insulin therapy, should monitor their glucose levels intensively, to assess glucose levels and take them into account when deciding on insulin doses, taking into account exercise and meal carbohydrate content. More and more continuous glucose monitoring systems (intermittent scanning or continuous glucose monitoring devices) are being used, and time in range (TIR) (Chapter 32) is rapidly becoming the standard to assess overall glucose levels.

To achieve strict glycaemic targets and avoid long-term hyperglycaemic complications, as supported in the Diabetes Control and Complications trial for type 1 diabetes [48] and later in the UK Prospective Diabetes Study for type 2 diabetes [55], pre-meal blood glucose readings should range between 4 and 7 mmol/l and post-meal levels from 4 to 10 mmol/l, with a value >7 mmol/l before bed. While individual specialists often follow their own dose adjustment algorithms, in general terms a change in dose of 2 units or 10% of a dose (whichever is the greater) is a sensible adjustment for most people taking insulin. A TIR (70–180 mg/dl; 4–10 mmol/l) of 70% is the target in most people living with type 1 diabetes [56].

Similar targets may be sought for people with type 2 diabetes, although trials based on achieving very tight HbA_{1c} targets, with some aiming for <6% (42 mmol/mol), serve to highlight the dangers of hypoglycaemia [57]. The frequency of blood glucose testing is extremely variable, with people being recommended to test anything from seven times a day down to four or five tests a week.

The most important aspect of regular self-monitoring by people on insulin is that the test result should be used as part of a management plan to help decide prospectively on insulin dose. There are, however, other points that should be considered when advising on when to self-test, including times of intercurrent illness to adjust insulin dose, symptoms and treatment of hypoglycaemia, driving, and foreign travel [58].

Place of insulin therapy in people with different types of diabetes

Insulin deficiency leads to hyperglycaemia, the hallmark of diabetes mellitus. Diabetes mellitus, however, comprises a heterogeneous group of diseases with regard to clinical presentation and progression. The classification of diabetes into type 1 diabetes and type 2 diabetes, which relies primarily on the presence or absence of autoantibodies against pancreatic islet β-cell antigens and age at diagnosis (younger for type 1 diabetes), is making room for a paradigm with a more individual assessment of remaining endogenous insulin production and insulin resistance [59].

Absence of endogenous insulin secretion, including type 1 diabetes

In people who are no longer producing endogenous insulin at levels that suffice to maintain normoglycaemia, such as people with type 1 diabetes or after total pancreatectomy, the administration of exogenous insulin is necessary to provide 24 h background and meal-time coverage, unless they are in the early stages of type 1 diabetes, have some residual β-cell function, or have been fortunate to become insulin independent following a pancreas or islet cell transplant. For many this coverage is provided by the *basal bolus regimen*, involving a combination of short- and long-acting insulin preparations. The advantage of such an approach is that it is generally better at providing a more physiological insulin replacement with a greater degree of 24 h flexibility than premix insulins injected once or twice daily. While it has the disadvantage of involving more daily insulin injections and requiring more frequent blood glucose monitoring, it provides a much greater degree of flexibility throughout the day. Importantly, for example, it allows the individual to vary the mealtime and size during the day to accommodate different daily activities and meal sizes. For some, this freedom is less important and the administration of only two injections a day sways them towards an insulin premix.

Insulin pumps can provide even more flexibility and responsiveness regarding glycaemia throughout the day and night. In case of pronounced diurnal variation in insulin sensitivity such as the *dawn effect* or related to intensive physical exercise, basal insulin infusion rates can be set and modified per hour, so that a more physiological insulin profile can be mimicked more closely than with the stable release of long-acting basal insulins. In specific circumstances, for example for children or for women attempting to become pregnant or who are pregnant, insulin pumps are becoming increasingly popular as a tool to achieve tight glycaemic levels. Furthermore, several novel *closed-loop* and *smart pump* devices enable automated reduction or increase in basal insulin delivery rate depending on the glucose level recorded by a coupled sensor; these devices have proven to be especially useful during the night [60, 61]. In addition, pumps may be more convenient to administer inter-meal correction bolus insulin or titrate the mealtime bolus to the anticipated carbohydrate load using the incorporated bolus calculators. The need to observe and react more directly with pump systems, however, requires more active involvement of the person with diabetes, while some people do not wish to have an external device and/or catheter attached to their body. Furthermore, pumps systems are more expensive (Chapter 33).

Insulin resistance and relative insulin deficiency, including type 2 diabetes

Exogenous insulin administration also has a place in the diabetes management of people with remaining, but insufficient, endogenous insulin production to cope with growing insulin resistance, such as those with type 2 diabetes or gestational diabetes. Insulin may be used with other anti-diabetes agents. Given the pandemic prevalence of type 2 diabetes, more people with type 2 diabetes use insulin than people with type 1 diabetes [62].

The recent European Association for the Study of Diabetes (EASD)/American Diabetes Association (ADA) consensus statement for type 2 diabetes treatment recommends choosing second-line therapies after metformin based on the presence of cardiovascular- and/or kidney-related comorbidities, risk of weight gain and hypoglycaemia, and cost [54]. Most guidelines worldwide recommend that people with established atherosclerotic cardiovascular disease, chronic kidney disease, or heart failure should be treated with a sodium glucose cotransporter 2 (SGLT-2) inhibitor or glucagon-like peptide 1 receptor agonist (GLP-1 RA). Consequently, the use of insulin in people with type 2 diabetes has been moved to later stages of the disease, as add-on therapy to other anti-diabetes agents. However, in case of obvious signs of catabolism, such as

unintentional weight loss, an HbA_{1c} higher than 10% (86 mmol/mol), or glucose levels higher than 300 mg/dl (16.7 mmol/l), insulin should be considered without delay.

Despite all guidelines giving clear indications on the importance of tight glycaemic levels, clinical inertia resulting in the delayed management of type 2 diabetes with insulin has been noted for decades. This clinical inertia involves not only the initiation of insulin therapy in people with type 2 diabetes and elevated HbA_{1c} despite other therapies, but also the intensification of insulin therapy [63]. For example, a real-world analysis of 6054 individuals with type 2 diabetes noted that insulin therapy was initiated at a mean HbA_{1c} of 10.1% (87 mmol/mol) [64]. In African American and Hispanic individuals with diabetes, the delay in insulin initiation might be even longer than in non-Hispanic white individuals [65]. In contrast, prompt intensive insulin therapy at the time of initial type 2 diabetes diagnosis when HbA_{1c} levels are higher than 9.0% (75 mmol/mol) might even improve β-cell function [66].

Often as type 2 diabetes progresses, the transition from oral anti-diabetes agents to insulin can be a time of stress and anxiety for many people for various reasons, including [67]:

- A sense of personal failure about being unable to *control* blood glucose levels with lifestyle, diet, and oral therapy.
- A feeling that the diabetes is much more serious than previously because it now requires injections rather than tablets.
- Apprehensions, fears, and very occasionally real phobias over the need to self-inject a treatment.
- Worries of hypoglycaemia leading to coma and death.
- Concerns over weight gain.
- Concerns that insulin may severely affect the individual's occupation and certain lifestyle activities.

With the increasing use of GLP-1 RAs, many people are now acquainted with injection therapy before exogenous insulin is needed. The advantages of injectable GLP-1 therapy are low risk of hypoglycaemia and less frequent, often only once-weekly, injection, which allows the person to become accustomed to the idea and technique of self-injection in a less frightening way. Nonetheless, we remain aware of the many anxieties insulin injections can induce.

Selecting the most appropriate insulin regimen: towards a personalized approach

Most people who have had either type 1 diabetes or type 2 diabetes try a number of treatment regimens throughout their lives. There are many factors that influence the decision to opt for a specific regimen and ultimately the most important is individual choice built on evidence from clinical trials. As insulin preparations have evolved from the early animal insulins to both human and analogue insulins, we have also seen the development of more versatile and indeed flexible treatment regimens that enable the doctor and nurse to provide the person with diabetes requiring insulin with a bespoke treatment that fits in better with their individual needs and lifestyle (Figure 31.9).

Intensive insulin therapy, combining mealtime and basal insulin preparations or pump therapy, is the standard of care in people with type 1 diabetes [68]. While in some people with type 2 diabetes insulin requirements are similar to those with type 1 diabetes, for many with type 2 diabetes insulin initiation and intensification is a more gradual process. Views differ on the insulin of choice for initiation, particularly as an add-on to other anti-diabetes agents. Supported by clinical trials, once-daily long-acting basal insulins are now recommended in type 2 diabetes treatment guidelines and have found significant popularity, particularly in the community as a means of introducing the person with type 2 diabetes to insulin [54]. Choosing basal insulin analogues over NPH is a matter of debate, mainly because of the higher costs that use of basal analogue insulins entails, despite that fact that clinical trials demonstrated lower rates of hypoglycaemia with long-acting basal analogues as an add-on to existing oral therapy compared to NPH insulin [69]. However, while basal insulin is a popular way of starting insulin, many people with diabetes do not achieve satisfactory glycaemic targets with this regimen and will require a second insulin injection with a mealtime component within 6–12 months [70].

In areas of the world with high carbohydrate intakes, starting insulin therapy with a combination of a basal and prandial component (often as basal plus, or as premix insulins), or even a prandial

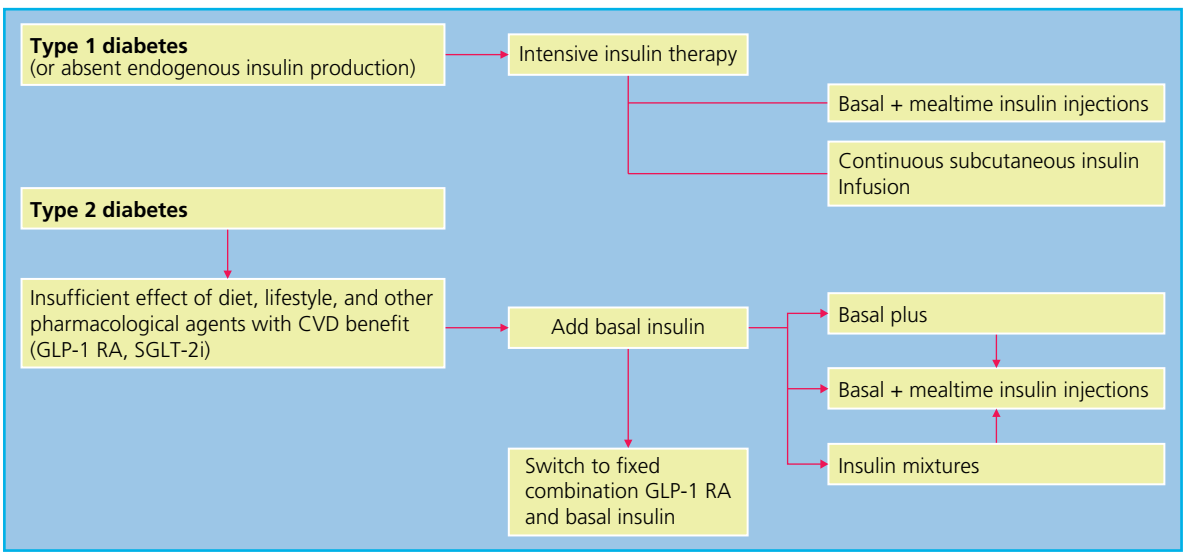

Figure 31.9 Suggested approach to selecting an insulin regimen in people with type 1 diabetes and 2 diabetes. CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SGLT-2i, sodium glucose cotransporter 2 inhibitor.

insulin regimen only, is popular. The relative merits of basal only, prandial only, and premix insulin have been evaluated [70,71]. Clearly there are advantages and disadvantages associated with each approach.

A pragmatic response is to consider the person with diabetes and their lifestyle, social circumstances, and comorbidities and take account of their likely long-term insulin needs. If it seems likely that the person will remain on a basal insulin as a single injection or as part of a future basal-bolus regimen, the basal insulin may be the best option. However, if it seems probable that the individual will be switched to a premixed insulin if a long-acting bolus does not achieve target, then initiating with a premixed insulin is a sensible alternative.

Basal only

One way in which insulin injections can be introduced to people with type 2 diabetes who are no longer able to manage their blood glucose with diet, lifestyle, and non-insulin anti-diabetes pharmacological therapies is to start with only one injection of insulin a day. This is usually added on to existing agents such as metformin, sulfonylurea, dipeptidyl peptidase 4 (DPP-4) inhibitors, SGLT-2 inhibitors, or GLP-1 RAs rather than as a replacement therapy. National and international guidelines in the UK, Europe, and the USA as well as the recent ADA/EASD consensus on glucose-lowering therapies in type 2 diabetes also recommend the use of a basal insulin with oral therapy as a way of initiating insulin in people with type 2 diabetes [54]. The initiation of insulin therapy, whether in the hospital or now more commonly in the community, should only take place within a structured programme employing active insulin dose titration. The program should include appropriate education; ongoing telephone, text, or email support; the use of glucose monitoring to inform dose titration to an agreed target; an understanding of diet; avoidance and management of hypoglycaemia; and support from appropriately trained and experienced healthcare professionals. Use of structured diabetes self-management education and support systems has proven to be very effective [53].

Some guidelines continue to recommend initiation with a human NPH insulin taken once or twice a day according to need [72]. However, many healthcare professionals are opting for long-acting insulin analogues, considering the reduced risk of (nocturnal) hypoglycaemia with these analogues. Also practicalities drive the preference for using basal insulin analogues with longer action profiles, particularly in people who require assistance with injections from a carer or healthcare professional and where the use of an analogue would reduce the number of injections from twice to once a day [23]. Similarly, indications for switching from NPH insulin to a long-acting basal analogue include not reaching an agreed HbA_{1c} target because of hypoglycaemia regardless of HbA_{1c}.

Most basal insulins are best administered before bedtime to reach the maximal effect during the night, thus achieving the primary goal of basal insulin, which is suppression of nocturnal hepatic glucose output and maintaining fasting glycaemia in an optimal way. When using the ultra-long insulin analogues, like U300 glargine or degludec, the timing of insulin administration is less crucial. Starting insulin doses can be calculated based on body weight (e.g. 0.1 unit/kg) or be standard (e.g. 10 units).

Once a basal insulin is started, it is important to adjust insulin doses appropriately to achieve an agreed target. Whereas the goal is to improve overall glycaemia, as measured by HbA_{1c}, the target to be used by individuals with diabetes and healthcare professionals to adapt the basal insulin dose is self-measured fasting glycaemia. Several algorithms have been developed to assist with this, almost all based on fasting blood glucose measured in the community and usually by the person with diabetes themselves [73–75]. Clinical inertia needs to be avoided and a reasonable, simple, but strict titration regimen should be agreed with the person with diabetes, in order to reach optimal glycaemic levels within an acceptable timeframe (e.g. titration twice a week). However, *over-basalization*, namely the blind up-titration of basal insulin doses without result, should be avoided. Indeed, once doses exceed 0.5 U/kg, the effects on glucose levels of increasing the insulin dose further are minimal, whereas their effect on weight gain continue. As a rule of thumb, when fasting glycaemia is within target but HbA_{1c} is not with basal insulin only, it is time to add mealtime insulin.

Basal plus

The addition of a fast-acting human insulin or rapid-acting insulin analogue prior to the main meal of the day can be a useful next step in intensification after starting a basal insulin in people with type 2 diabetes [76,77]. Increasingly healthcare professionals are prescribing rapid-acting insulin analogues over fast-acting human insulins [78,79]. The individual's dietary intake will determine which is the main meal and, therefore, with which meal the single injection of fast-/rapid-acting insulin will be given. Once again, it is important to titrate the prandial insulin to a glucose target. The ideal time to assess the impact of the prandial insulin, and certainly a rapid-acting insulin analogue, is 90–120 min after the meal. As with basal insulin adjustment, it is advisable not to change the insulin dose too frequently, ideally no less than twice a week. The person with diabetes may vary the amount of insulin administered based on the size of the meal, although as the insulin is given with the main meal of the day, the dose is usually fairly stable from one day to another. As glycaemic targets become more difficult to achieve, a second prandial insulin injection may be necessary, taken before the second main meal of the day using a similar dose titration procedure to that for the single prandial injection [80].

Insulin mixtures: premix insulins, combination insulins

As an alternative to the basal plus regimen, people with type 2 diabetes can change from a basal insulin to a mixed insulin formulation, which is given traditionally twice a day, with breakfast and the evening meal. This concept of premix insulins originated as a means of replacing the self-reconstituted combinations of regular insulin and NPH insulin and to cover the insulin needs for a typical Western diet with only two injections (30% regular insulin and 70% insulin NPH) [81]. However, such an approach does not mimic normal insulin physiology, and therefore increases the risk of hypoglycaemia [82]. Two types of pharmaceutical preparation have been developed to allow people with type 2 diabetes to harness the benefits of basal insulin action with other products, without increasing the risk of hypoglycaemia. The first is a combination of a basal and ultra-rapid insulin analogue (degludec and faster-acting insulin aspart, Rysodeg®, Novo Nordisk) and the second a combination of a basal insulin analogue and a GLP-1 RA (U100 glargine/lixisenatide, Suliqua®, Sanofi; degludec/liraglutide, Xultophy®, Novo Nordisk). In the case of the degludec/faster-acting insulin aspart combination, the advantage of the combination of a basal insulin and a mealtime insulin is maintained, with a lower risk of hypoglycaemia compared to standard premix insulins using NPH as the basal component. The combination of a basal insulin analogue and a GLP-1

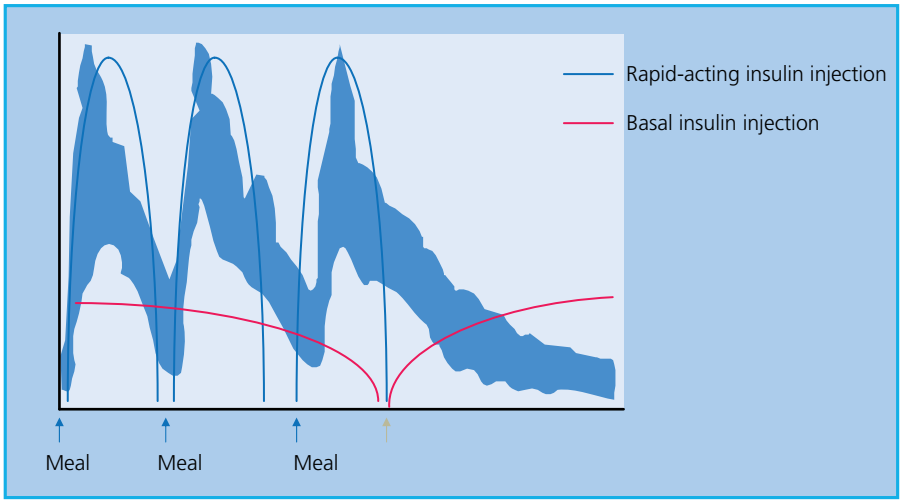

Figure 31.10 Schematic representation of the attempt to mimic physiological insulin release following three main meals using a basal-bolus regimen.

RA not only provides better overall glycaemic levels than basal-only insulins, but does so at a lower risk of hypoglycaemia and with less weight gain [83].

Basal bolus

Basal bolus is the most commonly used form of intensive insulin therapy in people with type 1 diabetes, but is also a popular regimen in people with type 2 diabetes where both mealtime and basal insulin components are needed.

The use of the basal bolus regimen in people with type 1 diabetes and type 2 diabetes attempts to mimic as closely as possible the normal physiological secretion of insulin by providing a background 24 h coverage of insulin by a basal insulin along with bolus injections at each meal (Figure 31.10). In most people with diabetes, with the development of long-acting analogue insulins the basal injection is administered once a day. However, based on the results of pre-meal self-monitored blood glucose values, some people may require two basal injections ~12 h apart to achieve satisfactory pre-meal glucose values without hypoglycaemia. Traditionally with NPH, basal injections are given in the evening, often before bed. However, this is less important with the basal insulin analogues and many people prefer to take their once-daily basal injection at the same time each morning. It is important that insulin doses are adequately titrated to achieve target glucose and HbA_{1c} values; for the basal bolus regimen the dose of the basal insulin is determined by measurement of fasting (pre-meal) glucose values, and the most appropriate fast human or rapid-acting analogue insulin dose is best determined by two-hour post-prandial glucose values.

More practical tips on starting and titrating insulin

In the past, particularly for people with type 1 diabetes, insulin initiation was conducted either as an inpatient or as a day case in a hospital diabetes centre. As confidence grew with the development of purer animal insulins and most recently with human and analogue insulins and the introduction of disposable syringes, pen injectors, and needles, more insulin starts are performed as an outpatient. Lately, with an increased emphasis on community-based diabetes care, insulin initiation, particularly in people with type 2 diabetes, is taking place in health centres and general practitioner surgeries [84]. While older algorithms for helping to decide when and where insulin should be initiated have been published, national and local guidelines now seem more appropriate as varying levels of expertise, infrastructure, and service delivery are present in different areas of the world.

In order to achieve a successful insulin initiation, it is vital that a good insulin initiation programme is in place, with a qualified and competent diabetes nurse specialist. Several programmes are available, most with appropriate training courses for healthcare professionals. Insulin initiation involves much more than teaching someone how to use a needle and syringe, and the process of starting and successfully stabilizing them on insulin will require several structured contacts with the nurse and also a 24 h emergency contact number for any urgent problems that may arise (Table 31.1).

For those presenting acutely ill with nausea and vomiting with or without ketosis, admission to hospital for insulin initiation and, where needed, intravenous fluids is a necessity.

Future perspectives: route, hepatoselectivity, glucose-dependent action

From the early days of insulin, alternatives to the classical parenteral route of insulin administration have been explored. Although inhaled insulin is available, the quest for oral insulin has never stopped. Structural modification and the use of innovative pharmaceutical formulations such as nanoparticles encapsulating the insulin to engender resistance to degradation have been investigated [85]. In 2019, a long-acting, basal insulin analogue formulated in a tablet with the absorption-enhancer sodium caprate, called oral insulin 338, was found to improve glycaemic levels in insulin-naïve individuals similar to subcutaneously administered insulin glargine [86]. Further development of this particular oral insulin project was discontinued because the doses were high, and therefore production for wide public use was deemed not commercially viable. Recent encouraging developments in oral peptide hormone administration in the GLP-1 RA arena (oral semaglutide using salcaprozate sodium [SNAC] technology) have boosted the research efforts towards

Table 31.1 An example of an outpatient/community pathway for people starting insulin for the first time.

Session 1
The need for insulin has already been discussed with the person with diabetes by a doctor or diabetes nurse specialist and the person with diabetes has been seen by a dietician
A regimen has been agreed and the first prescription has been obtained by the person with diabetes
A review usually takes place of what diabetes is, including what insulin does and the need for insulin injections
A nurse demonstrates the basics and use of an insulin injection device and the person with diabetes gives the first injection
Further discussions including: • sites for injection/site rotation • timing of injections • where and how to obtain equipment (insulin, pens, needles, self-monitoring equipment, sharps disposal equipment) • recognition and management of hypoglycaemia and hyperglycaemia (in type 1 diabetes importance of ketones) • self-blood glucose monitoring • driving and legal issues surrounding insulin • 24 h contact details provided
Session 2 (around 2 wk after insulin initiation)
Prior to session 2, the person with diabetes and the nurse will usually have had telephone contact over insulin injections and blood glucose readings
Review of information provided in session 1
Review of insulin injection technique
Session 3 (around 4 wk after insulin initiation)
Review of sessions 1 and 2
Further information provided about: • insulin on holiday and when travelling • insulin injections when travelling through time zones (e.g. transatlantic travel) • insulin management during periods of acute sickness • foot care, other diabetes-related complications, and, in women of child-bearing potential, pregnancy
Session 4 (around 10 wk after insulin initiation)
Review of previous sessions
Assessment of glycaemic control and need for further doctor/nurse follow-up
Book follow-up clinic/surgery appointment

the development of oral insulin preparations [87]. However, the hurdles remain numerous, such as low bioavailability, interference with food intake, and in particular the narrow dosing range of insulin.

Another unmet need in insulin therapy is the hepatoselectivity of the preparations. It is important to appreciate that in health, pancreatic-derived insulin acts directly on the liver via the portal circulation. In the fasting state, a major function of insulin is to suppress hepatic glucose production. Between 50% and 80% of the insulin is metabolized by the liver [88], such that much lower and tightly regulated insulin levels enter the systemic circulation. Peripheral tissues such as muscle also take up glucose at higher insulin concentrations, which tend to occur predominantly postprandially. The administration of insulin by subcutaneous injection delivers it to the systemic circulation, with relatively lower levels reaching the liver. Therefore, glucose uptake by muscle and adipose tissue is preferential to liver. The lower exposure of the liver to insulin also results in greater hepatic glucose production, making the management of blood glucose and body weight even more challenging.

An initial approach to targeting insulin action to the liver was through the development of hepatoselective insulins [89], including the technique of making the insulin molecule larger through PEGylation to favour its leaving the circulation at the hepatic sinusoids. The first trials with insulin peglispro resulted in a reduction of HbA_{1c} and body weight [90]. However, insulin peglispro also caused elevated transaminase and triglyceride levels, resulting in the early termination of its development [91]. Currently, other approaches such as an insulin analogue with a C20 fatty diacid attached at position A22K (NNC0123-0327) is under investigation; this insulin has a high affinity for serum albumin and reduced trans-endothelial transport from plasma to periphery, which could result in high clearance via the hepatic insulin receptors [92]. Safety will have to be proven, particularly regarding steatohepatitis and hypoglycaemia, before these products could gain market access.

Finally, the ultimate dream of insulin development is the realization of a glucose-dependent insulin action. Several paths are explored, ranging from glucose-responsive polymer encapsulation of insulin to molecule modifications [93].

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32 New Technologies for Glucose Monitoring

Thomas Danne and Olga Kordonouri
Diabetes Center, Children's Hospital AUF DER BULT, Hannover Medical School, Hannover, Germany

Key points

- Continuous glucose monitoring (CGM) is becoming the gold standard for metabolic monitoring and is increasingly replacing blood glucose monitoring for everyday treatment decisions.
- Time in range and time below range complement glycated haemoglobin (HbA_{1c}) as measures of glycaemic regulation in type 1 diabetes.
- Standardized analysis of CGM values includes visualization of data with software solutions like the ambulatory glucose profile (AGP).
- Algorithms for automated insulin delivery combining glucose sensors and insulin pumps (hybrid closed loop) or smart pens, as well as artificial intelligence based on analysis of CGM values, are becoming commercially available.

Until recently, regular self-measurement of capillary blood glucose was an indispensable part of good metabolic management. Following the early days of urinary glucose determination for metabolic monitoring, the introduction of capillary blood glucose monitoring in the 1960s was instrumental in improving glycaemic management in people with diabetes (Figure 32.1). Blood glucose monitoring technology has improved considerably in recent years. Innovation in blood glucose monitoring devices and strip technology has brought significant advances in the reliability of measurement and operation of these systems. Comparable to the introduction of capillary blood glucose monitoring more than 50 years ago, continuous glucose monitoring (CGM) systems have significantly and positively influenced the glucose monitoring of people with diabetes in a short time and can contribute to a further improvement of metabolic management [1]. Modern programs and interfaces to computers and smartphone apps offer a wide range of display and analysis functions, including insulin dose calculation. Glucose monitoring is an essential part of the therapy of insulin-treated diabetes.

Glycated haemoglobin (HbA_{1c}) has become established as a target measurement for long-term glucose management [2] and is considered a surrogate for optimal glycaemic levels and treatment success in international diabetes guidelines [3]. However, because HbA_{1c} represents the average blood glucose concentration over the past 8–12 weeks [2], it does not capture *short-term* blood glucose fluctuations such as hypoglycaemia and post-prandial hyperglycaemia [4]. A primary goal of insulin therapy in diabetes has been to optimize glycaemic levels by reproducing the physiological insulin release that is seen in response to glucose and other stimuli when the pancreatic islets are functioning normally [5]. Recent developments in glucose measurement, insulin delivery, algorithms that relate these two processes, and data management software to demonstrate glycaemic patterns have shown the potential to improve the lives of people with diabetes. This chapter reviews the current status of these developments, and their use in the management of insulin-treated diabetes.

Self-monitoring of capillary blood glucose

Self-monitoring of capillary blood glucose has been considered an essential component in the treatment of type 1 diabetes since the Diabetes Control and Complications Trial (DCCT) [6]. Capillary blood glucose monitoring is also indicated for people with insulin-treated type 2 diabetes and may, when prescribed as part of a broader educational context, be helpful for other people with type 2 diabetes when used to guide treatment decisions or self-management [3]. The further development of the lancing devices and lancets on the market today has also made multiple daily blood glucose self-measurements tolerable and feasible. All lancing devices are based on the principle that the penetration depth of the respective lancets into the skin can be controlled. In addition, pain can be further reduced by choosing particularly thin lancets. Technical improvements in blood glucose meters in recent years include lower blood volume, higher measurement accuracy, lower susceptibility to interference, and better data display.

The preparatory steps for blood glucose monitoring, in particular obtaining a capillary blood drop, as well as correctly performing the actual measurement require theoretical and practical training. Ideally, this should be done using the system that the person with diabetes will later use. A one-off introduction is often not enough: the various steps should be repeatedly trained, discussed, and closely supervised. Since performing capillary blood glucose monitoring in public (school, workplace, restaurant, etc.) makes it visible that the person has diabetes, people often do not perform measurements in such situations. This can entail significant risks, as acute glucose derailments remain undetected. The understandable desire of the person with diabetes for discretion makes other glucose monitoring options attractive. However, not all people with diabetes want to wear a technical device permanently on their body or be disturbed by alarms.

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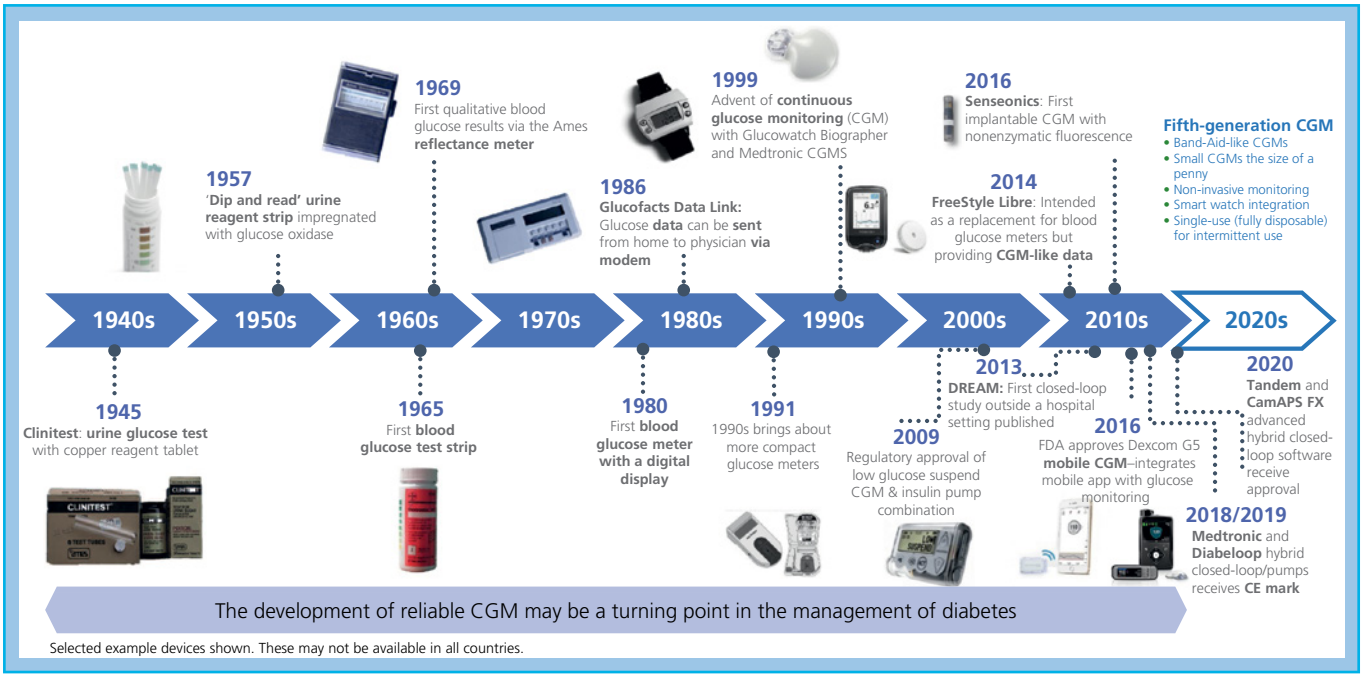


Figure 32.1 History and immediate future of glucose monitoring.

Measurement method and frequency

The enzyme used in capillary blood glucose monitoring systems is usually either glucose oxidase (GOD) or glucose hydrogenase (GDH). The glucose oxidase method is susceptible to substance and drug interferences (e.g. ascorbic acid, paracetamol, blood oxygen content) and these should be considered, especially in people with multimorbidities. For those with high or low haematocrit values, the manual or test strip package insert of the monitoring systems should be checked for compatibility.

People with type 1 diabetes using multiple daily injections or an insulin pump should measure the blood glucose concentration at least four times daily (before meals and at bedtime) and every 2–3 weeks during the night. In addition, measurements may be taken in special situations, for example to check the effects of meals, in suspected hypoglycaemia, during sport, illness, holidays, or when driving a car. People with type 2 diabetes using multiple daily injections should also determine pre-prandial and occasionally post-prandial glucose levels and measure before bedtime. People with type 2 diabetes treated with sulfonylurea require test strips to detect hypoglycaemia. There is a rationale to provide all people with type 2 diabetes and oral anti-diabetes therapy with at least 50 test strips per quarter in case of intercurrent illnesses, for training purposes, or if the treatment goals are not met. Women with gestational diabetes should always measure fasting blood glucose and post-prandial glucose 2–3 times per day.

Systems and measurement quality

There are many different capillary blood glucose monitoring systems currently available from various suppliers. Overviews of the properties of these systems are primarily based on the information provided by the manufacturers. Many modern capillary blood glucose monitoring systems have additional functions, such as data storage and read-out, marking of values as pre-prandial or post-prandial, colour coding of displayed values for immediate assessment, a light at the test strip slot, bolus calculators, calculation of an estimated HbA_{1c} value, or the possibility of transmitting data to an app or internet cloud (connectivity).

Table 32.1 Comparison of ISO 15197:2013 and US Food and Drug Administration (FDA) blood glucose (BG) meter accuracy standards.

Setting	FDA	ISO 15197:2013
Home use	95% within 15% for all BG in the usable BG range[a] 99% within 20% for all BG in the usable BG range[a]	95% within 15% for BG ≥100 mg/dl 95% within 15 mg/dl for BG <100 mg/dl
Hospital use	95% within 12% for BG ≥75 mg/dl 95% within 12 mg/dl for BG <75 mg/dl 98% within 15% for BG ≥75 mg/dl 98% within 15 mg/dl for BG <75 mg/dl	99% in A or B region of consensus error grid[b]

To convert mg/dl to mmol/l, divide by 18.018. BG, blood glucose.
[a] The range of blood glucose values for which the meter has been proven accurate and will provide readings (other than low, high, or error).
[b] Values outside of the 'clinically acceptable' A and B regions are considered 'outlier' readings and may be dangerous to use for therapeutic decisions.

Currently, all capillary blood glucose monitoring systems approved for commercial use in Europe must comply with ISO 15197:2013 in terms of measurement accuracy (Table 32.1) [7]. The new ISO 15197:2013 defines stricter quality standards for blood glucose measurement: for example, readings above 100 mg/dl (5.6 mmol/l) may only deviate by 15% compared to a laboratory reference method. For blood glucose values below 100 mg/dl (5.6 mmol/l), 95% of the measured values must lie within a range of ± 15 mg/dl (0.83 mmol/l). The preface and annex of the DIN

standard have been revised and are now called DIN EN ISO 15197: 2015-12. For glucose meters used at home, the US Food and Drug Administration (FDA) guidance specifies the following accuracy standards [8]: 95% of all measured blood glucose meter values must be within 15% of the true value from a laboratory measurement; and 99% of meter values must be within 20% of the true value. Notably, these new FDA standards require greater hypoglycaemia accuracy than the 2013 ISO standard, which is used outside the USA.

Quality control for personal glucose measurement systems can be performed with a system-specific control solution. More than 90% of incorrect measurement results are due to operating errors: unclean hands, incorrectly stored or damaged test strips, and insufficient blood volumes. Therefore, careful training of people with diabetes and all other caregivers in the use of capillary blood glucose monitors is essential.

Continuous glucose monitoring

Systems for continuous measurement of interstitial glucose are offered in various technical designs (Tables 32.2 and 32.3). Continuous glucose monitoring in *real time* (rtCGM) provides contemporaneous subcutaneous glucose data [9, 10]; intermittently scanned CGM (isCGM, *flash glucose monitoring*) [11, 12] uses a comparable methodology to show continuous glucose measurements currently and retrospectively at the time of review (Figure 32.2). With isCGM, the current glucose level is displayed only with an active scan of the reader over the sensor, along with a trend arrow and an eight-hour history graph. It is difficult for people working outside the field of diabetes to differentiate between technologies, such as calibrations, alarms, practicalities of attaching and wearing sensors, or costs, which are device specific. Because these technological details are subject to constant change, the term CGM is used to refer to all aspects related to the device class unless otherwise noted [13].

rtCGM systems can be used either as stand-alone devices, for instance for people with diabetes with multiple daily injections, or in combination with an insulin pump. In sensor-augmented pump therapy, the rtCGM system can be programmed to communicate with the pump for automated insulin dosing (AID) to suspend insulin at a certain glucose threshold or predictive low glucose suspension. The system can be used to prevent hyperglycaemia, by automated adaptation of the basal rate or automated correction boluses. Almost all rtCGM systems allow the measured values to be transferred to a cloud. From there, the data can be forwarded to family members or the diabetes team if so desired.

Table 32.2 Types of continuous glucose monitoring (CGM) systems.

Type of CGM	Description
Real-time CGM (rtCGM)	CGM systems that measure and display glucose levels continuously
Intermittently scanned CGM (isCGM)	CGM systems that measure glucose levels continuously, but only display glucose values when swiped by a reader or a smartphone
Professional CGM	CGM devices that are placed on the person with diabetes in the healthcare professional's office (or with remote instruction) and worn for a discrete period of time (generally 7–14 d). Data may be blinded or visible to the person wearing the device. The data are used to assess glycaemic patterns and trends. These devices are a clinic-based device, as opposed to the patient-owned rtCGM/isCGM devices.

Continuous glucose monitoring measurement method

In most of the currently available transcutaneous needle sensors, glucose is measured using an enzymatic method, such as glucose oxidase, in the interstitial fluid of subcutaneous fatty tissue (Figure 32.3b). The measurement signal is an electrical current. That current is proportional to the glucose concentration at the measurement site, with a small background current, which can be accounted for as a signal offset if necessary. The transcutaneous rtCGM systems have a lifecycle of up to 10 days, after which the glucose sensor should be replaced according to the manufacturer's instructions. The sensors normally transmit an average value obtained every five minutes to the corresponding receiving device. As with blood glucose measuring systems, medication can result in interferences (e.g. paracetamol; see device operating instructions). Some systems are factory calibrated [14], while others need daily calibrations with capillary blood glucose measurement to account for sensor drift.

In addition, a long-term rtCGM system is available in which the sensor is inserted under the skin with minimal surgical intervention (Figure 32.3a). This implantable long-term CGM system comprises a wireless, subcutaneously implantable glucose sensor and a body-worn transmitter with on-body vibration alarm capability. The sensor is constructed of a fluorescent, boronic acid–based glucose-indicating polymer coated onto a miniaturized, polymer-encased optical detection system [15]. The external transmitter wirelessly communicates with and powers the sensor and contains Bluetooth capability for interfacing with a smartphone application. The sensor needs daily calibrations and is removed by a certified physician after its functional period of up to 180 days. The insertion and removal procedure from the subcutaneous location (upper arm) can be done in a brief outpatient procedure. As the glucose measurement is fluorescence based, it can lead to short-term measurement interruptions, especially at the beginning during bright sunlight.

Intermittently scanned continuous glucose monitoring

The use of isCGM incorporates trend displays of the currently scanned glucose value and the presentation of retrospective CGM data to help achieve therapy goals. Similar to capillary blood glucose monitoring, the success of isCGM depends on the user being active. With the second generation of devices, it has become possible to turn on threshold limit alarms (hypo- and hyperglycaemia alarms). The high and low alarms are distinguished by acoustically different alarm tones and scanning displays the current measured value. The third generation offers continuous Bluetooth connectivity to a smartphone app.

Like with all factory-calibrated devices, people with diabetes can largely do without capillary blood glucose monitoring. Blood monitoring is advised, however, if hypoglycaemia symptoms do not match the isCGM values and the glucose trend displayed, or very high glucose values or strong glucose fluctuations are present. Sensor artefacts can occur as a result of lying on the sensor while

Table 32.3 Overview of commercially available continuous glucose monitoring (CGM) devices (available in Germany as of January 2023).

CGM model	Approved age group	Lifecycle per sensor	Connectivity, smartphone/ wearable	Connectivity to automated insulin delivery	Calibration with blood glucose	Initialization phase	Recommended place of insertion	Glucose display	Glucose range	Low alarm	Replacement claim for blood glucose measurements
Abbott FreeStyle Libre	From 4 yr	Up to 14 d	Android and iOS app, Follower app	No	Factory calibrated	1 h	Upper arm	After scan, every min	40–500 mg/dl 2.2–27.7 mmol/l	No	Yes
Abbott FreeStyle Libre 2	From 4 yr	Up to 14 d	Android and iOS app, Follower app	No	Factory calibrated	1 h	Upper arm	After scan, every min	40–500 mg/dl 2.2–27.7 mmol/l	Yes	Yes
Abbott FreeStyle Libre 3	From 4 yr	Up to 14 d	Android and iOS app, Follower app	Yes (Ypsopump with CamAPS FX app)	Factory calibrated	1 h	Upper arm	No scanning, every min to smartphone app	40–500 mg/dl 2.2–27.7 mmol/l	Yes	Yes
DexCom G6	From 2 yr	Up to 10 d	Android and iOS app, Follower app, smartwatch app	Yes (Tandem T-slim with control IQ; Ypsopump with CamAPS FX app)	Factory calibrated, optional	2 h	Abdomen, (children, adolescents 2–17 yr: upper buttocks)	Every 5 min	40–400 mg/dl 2.2–22.2 mmol/l	Yes	Yes
DexCom G7	From 2 yr	Up to 10 d	Android and iOS app, Follower app, smartwatch app	Not yet	Factory calibrated, optional	30 min	Abdomen (children, adolescents 2–17 yr: upper buttocks)	Every 5 min	40–400 mg/dl 2.2–22.2 mmol/l	Yes	Yes
Medtronic Guardian 3	Without age limit	Up to 7 d	iOS app, Follower app	Yes (Medtronic 640G, 670G, 770G, 780G)	2 h, 8 h after insertion, then every 12 h	2 h	Abdomen, buttocks (upper arm)	Every 5 min	40–400 mg/dl 2.2–22.2 mmol	Yes	No
Medtronic G4	Age 7 (with 780G)	Up to 7 d	iOS app, Follower app	Yes (Medtronic 780G)	Factory calibrated, optional	2 h	Abdomen, buttocks (upper arm)	Every 5 min	40–400 mg/dl 2.2–22.2 mmol	Yes	Yes
Medtrum A6 touch Care	From 2 yr	Up to 7 d	Android and iOS app, smartwatch app	Yes, patch pump with low glucose suspend	Every 12 h	2 h	Upper arm, abdomen, buttocks, abdomen	Every 2 min	40–450 mg/dl 2.2–25 mmol/	Yes	No
Menarini GlucoMen Day CGM	From 6 yr	Up to 14 d	Android and iOS app	No	Every 24 h	45 min	Abdomen	Every min	40–400 mg/dl 2.2–22.2 mmol/	Yes	Yes
Senseonics Eversense	From 18 yr	Up to 180 d	Android and iOS app, Follower app, smartwatch app	No	4× every 2 h after insertion, then every 12 h	24 h	Implanted (upper arm)	Every 5 min	40–400 mg/dl 2.2–22.2 mmol/	Yes	No

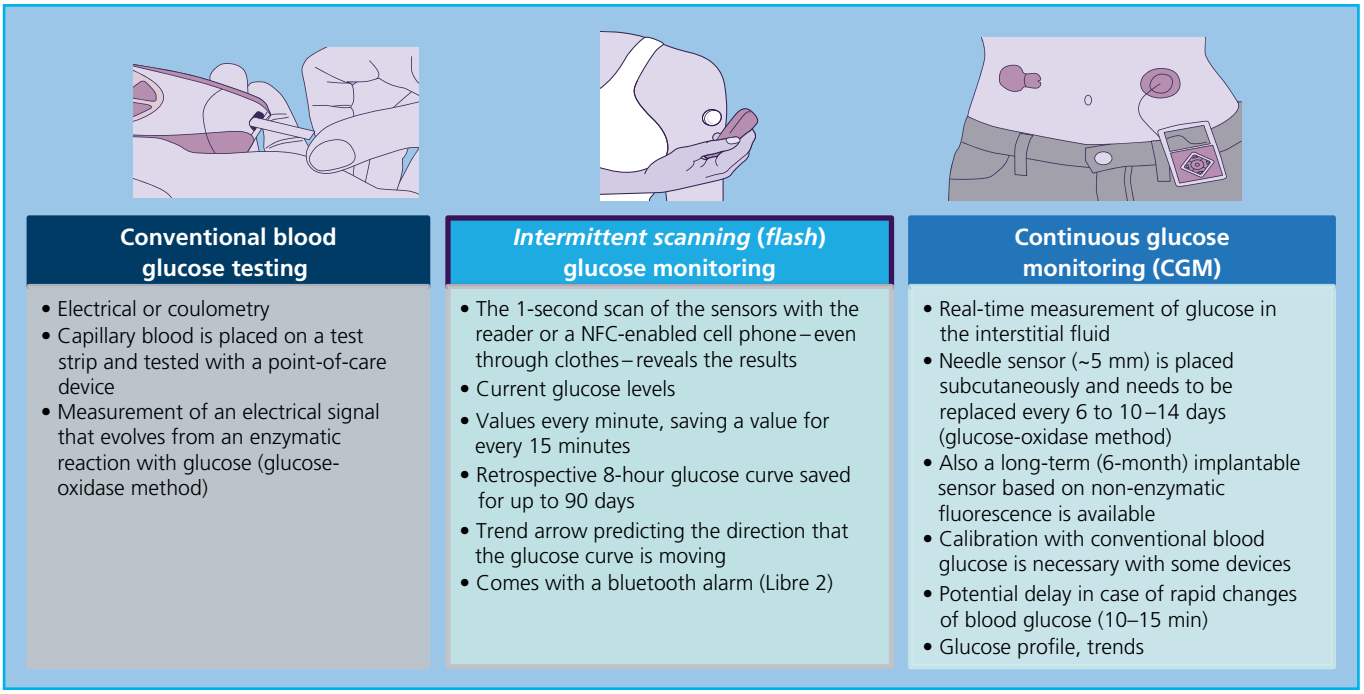


Figure 32.2 Overview of current technologies for measuring glucose in blood or the interstitial fluid. NFC, near-field communication.

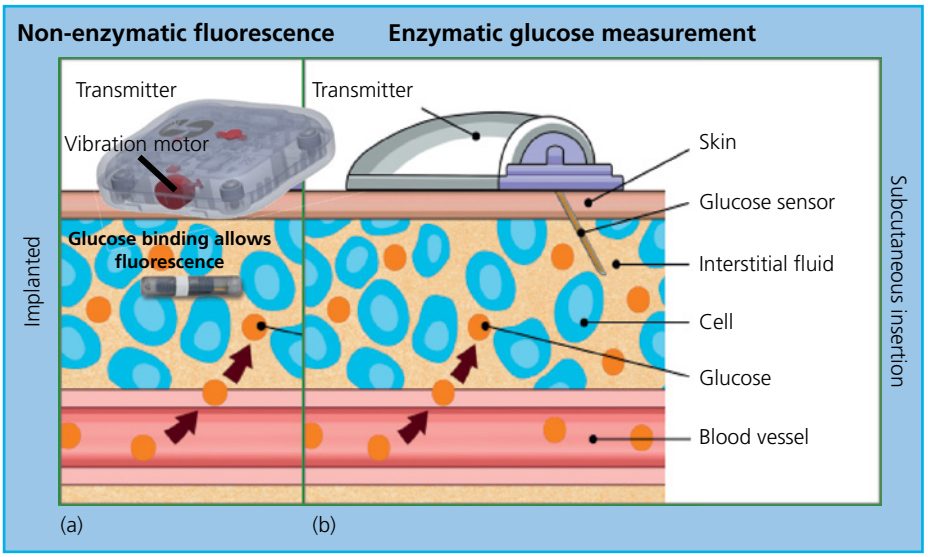


Figure 32.3 Principles of interstitial glucose monitoring. (a) Implantable long-term sensor (modelled from the Senseonics device) where glucose is measured with non-enzymatic fluorescence and an on-body transmitter that vibrates at threshold glucose levels. (b) Model of a subcutaneous electrochemical needle sensor that needs to be changed every 1–2 weeks with a transmitter corresponding to a dedicated scanning device (intermittently scanned continuous glucose monitoring, isCGM) or continuously to a receiver that could be a smartphone app, handheld, or pump (real-time continuous glucose monitoring, rtCGM).

sleeping; this also applies to rtCGM systems with needle sensors. This leads to apparent long hypoglycaemic episodes that have not actually occurred. isCGM systems require additional training similar to rtCGM systems.

Minimal requirements for continuous glucose monitoring performance

In contrast to factory-calibrated systems, the accuracy of systems that require user calibration is dependent on capillary blood glucose testing. Therefore, for these it is important to have an accurate glucose meter. Successful calibration also requires several conditions (Box 32.1).

The *mean absolute relative difference* (MARD) is currently the most common metric used to assess the performance of CGM [16]. MARD is the average of the absolute error between all CGM values and matched reference values. A small percentage indicates that the CGM readings are close to the reference glucose value, whereas a larger MARD percentage indicates greater discrepancies between the CGM and reference glucose values. This value determined in clinical studies is significantly influenced by the study protocol and the selection of the people with diabetes examined. The MARD value should therefore only be used as a guide [16]. Another parameter that deals with the measurement quality of a CGM system is the *precision absolute relative deviation* (PARD), calculated

Box 32.1 Teaching points for individuals with diabetes: calibration dos and don'ts.

- *Do* follow the manufacturer's instructions regarding the time and frequency of calibration to achieve the greatest possible accuracy.
- *Do* use only very recent blood glucose measurements for calibration.
- *Don't* calibrate when the blood glucose is changing at a significant rate, as indicated by trend arrows on the display. Times when rapid blood glucose change may occur include:
  - Within 3–4 hours of a meal or an insulin bolus.
  - During exercise.
  - When recovering from hypoglycaemia.

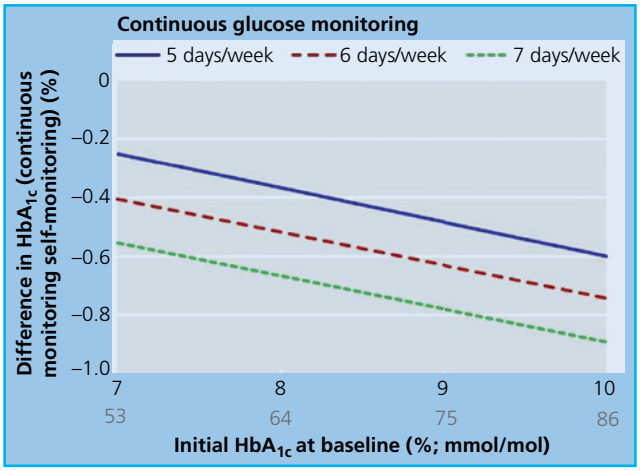


Figure 32.4 Device use is important for the success of continuous glucose monitoring (CGM). A model of the estimated relation between the difference in effect of CGM compared with capillary blood glucose monitoring and baseline glycated haemoglobin (HbA_{1c}) values for different sensor usages for an example 40-year-old with type 1 diabetes. Source: Modified from Pickup et al. 2011 [18].

simultaneously for the same person from the direct comparison of an rtCGM system with a second sensor from the same system [16].

Although controversy exists regarding the exact cut point for accuracy, *in silico* testing has shown that a further lowering of MARD below 10% from reference values has little additional benefit for insulin dosing [17].

Clinical efficiency of continuous glucose monitoring

Numerous studies have shown that use of CGM improves glycaemic levels and quality of life in both children and adults with type 1 diabetes treated with pumps or multiple daily insulin injection therapy, improving HbA_{1c}, shortening the time spent in hypoglycaemia and hyperglycaemia, and reducing moderate to severe hypoglycaemia [9, 13, 18]. CGM use also benefits individuals with type 2 diabetes who are managed with or without intensive insulin treatment [4]. There are limited data regarding the benefit of rtCGM as an outcome measure for individuals with gestational diabetes (GDM) and type 2 diabetes, especially in those who do not use insulin [4]. The benefit of rtCGM is directly correlated to persistence and frequency of use. A meta-analysis by Pickup et al. found that every one day increase of sensor usage per week increased the effect of CGM; the effect on HbA_{1c} is more pronounced with higher initial HbA_{1c} (Figure 32.4). For retrospective analysis and counselling, a minimum of 14 consecutive days of data with approximately 70% of possible CGM readings appears to generate a report that enables optimal analysis and decision making. Standard reporting and visualization of CGM data are important [13, 19].

As the consequences of increased glycaemic variability adversely affect people with type 1 diabetes both physically and mentally [13, 20–23], people with diabetes report that the use of CGM leads to improved diabetes-specific quality of life through reduced variability of glucose values and additional subjective safety with regard to hypoglycaemia. Many individuals also experience improved general well-being and performance in many areas of life [24, 25] (Figure 32.5).

Practical issues with the use of continuous glucose monitoring

Calibrating the sensor

Some of the currently available CGM devices are calibrated using finger-stick capillary blood glucose measurements, while others are factory calibrated and no longer need calibration [14]. To optimize sensor accuracy, it is important that the device is calibrated only when the glucose level is relatively stable, and there is steady-state equilibration between glucose concentrations in the blood and interstitial fluid. In practice, calibrations should be performed preprandially or at least three hours after a bolus (Box 32.1). Each manufacturer's instructions should be consulted to determine the timing and frequency of calibration for a specific CGM device.

Physiological lag between blood and interstitial glucose

The lag in the equilibration of glucose levels between the capillary blood and the interstitial fluid in the subcutaneous tissue (measured by the CGM device) has important practical implications. In general, increases or decreases in the glucose concentration will first be apparent in the blood followed by the interstitial fluid. This physiological lag has implications with regard to the detection and treatment of hypoglycaemia. Because of the lag of interstitial glucose behind blood glucose, when the glucose level is declining the interstitial (sensor) glucose can be in the normal range even though the actual blood glucose is low. This can occur with the newer generation of devices and is particularly pertinent during exercise [26]. Users should be instructed to perform a capillary blood glucose measurement before driving if the sensor glucose reading is normal and the trend graph or rate-of-change arrows on the sensor display indicate that the glucose level is declining (Box 32.2). The practical implication is that if the person feels hypoglycaemic or has reason to suspect that the glucose is declining, but this is not corroborated by the sensor, they should disregard the sensor data and carry out a capillary blood glucose measurement.

This lag phenomenon also has practical implications for the treatment of hypoglycaemia. During recovery from hypoglycaemia, the increase in the interstitial glucose will often lag behind the blood glucose [27], and when blood glucose has already normalized the sensor (interstitial) glucose may still be low. Individuals should be informed of the need to perform capillary blood glucose measurements to assess the response to treatment of hypoglycaemia accurately. Those who rely on the rtCGM to judge whether the glucose level is improving following ingestion

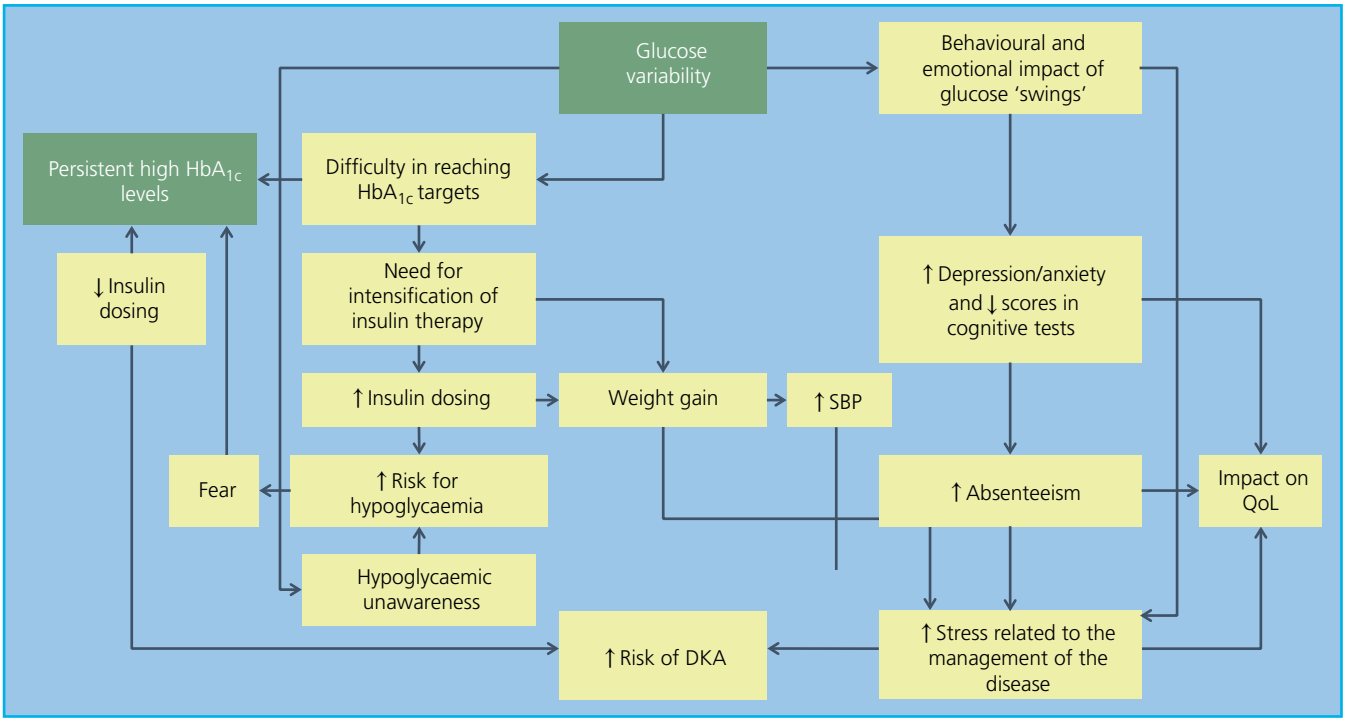


Figure 32.5 Consequences of increased glycaemic variability for people with diabetes. DKA, diabetic ketoacidosis; HbA_{1c}, glycated haemoglobin; QoL, quality of life; SBP, systolic blood pressure.

Box 32.2 Teaching points for individuals with diabetes: circumstances where capillary blood glucose must be checked

- If the sensor indicates that the glucose is elevated, the reading should be confirmed with a capillary blood glucose measurement before the person takes a corrective bolus.
- When subjective symptoms are not in keeping with the sensor reading, such as a low continuous glucose monitoring (CGM) reading in the absence of hypoglycaemic symptoms, a capillary blood glucose reading should be taken to confirm the glucose level.
- Before or during driving, if the sensor reading is normal but the CGM rate of change indicator or tracing indicates that the glucose level is falling, the person should measure capillary blood glucose.
- Following treatment of a low glucose level, if the sensor still shows a low reading, the person should check capillary blood glucose and use this measurement to decide whether to take in more carbohydrate. Reliance on the sensor reading to assess response can lead to overtreatment.

of carbohydrates may mistakenly assume that they need to consume more glucose than necessary.

Trend arrows

Trend arrows allow an estimation of the rate of change of glucose. With this information, a single glucose value can be correctly classified for the first time and a sensible therapy adjustment can be made, for instance percentage lowering or increasing of a basal rate, or eating carbohydrates, or insulin correction. The classifications of the trend arrows vary according to the manufacturer. Although CGM measuring devices have a comparable graphical representation to inform the user about changes in glucose values, there is no uniform basic grid regarding the relationship between the rate of change and the positioning of the arrows [28]. General recommendations for therapy decisions need to consider both the trend arrows and the current prevailing glucose levels.

Ultimately the use of trend arrows for treatment decisions has to be adapted individually and various approaches have been suggested. The recommendation of the Juvenile Diabetes Research Foundation (JDRF) and the Diabetes Research in Children Network Study Group (DirecNet) suggest a percentage adjustment of the insulin dose according to the trend arrows to a maximum of 20%. According to their studies with different patient groups and therapeutic regimens, people with diabetes often make significantly higher insulin dose adjustments, well beyond these recommendations, based on the trend arrows. In these studies, which are based on self-completed questionnaires, people with diabetes reported that the insulin dose may be increased by more than 100% when the trend is rising, but the insulin dose is only reduced by a maximum of 50% when the trend is falling [29]. As a result, another approach recommends that a certain, absolute amount of glucose is added or subtracted from the current glucose value in accordance with the trend arrows for calculating the correction bolus. However, this approach requires a high degree of numeracy on the part of the person with diabetes and may lead to an additional burden [30].

A simpler model for using the rate-of-change information with trend arrows assumes that the glucose value, depending on the trend information, changes by 67 mg/dl (3.7 mmol/l), 112 mg/dl (6.2 mmol/l), or at least 135 mg/dl (7.5 mmol/l), rising or falling respectively within the next 45 minutes. An easily applicable addition or subtraction template for correcting the insulin bolus is suggested: 1, 1.5, or 2 insulin units depending on the trend arrow

information [31]. This simplifies the calculation of the insulin dose, but can only be used for a small group of people with diabetes, since it does not take into account individual insulin therapy, insulin sensitivity, or other clinical characteristics of the person with diabetes. Thus, other proposals recommend an adjustment based on insulin units depending on different levels of insulin sensitivity, and differentiates between children and adults [32, 33]. Ziegler et al. synthesized these recommendations in a clear, colour-coded, tabular format, aiming to provide CGM users with a personalized and simplified system of scorecards for daily use [28].

Setting of glucose alarms

The alarms for hypoglycaemia and hyperglycaemia are an important feature of CGM devices. There are trade-offs in the adjustment of alarm thresholds, and settings need to be individualized based on specific clinical considerations [34]. If the alarm thresholds are set at target or ideal glucose levels (e.g. low = 5 mmol/l [90 mg/dl]; high = 10 mmol/l [180 mg/dl]), there will be increased sensitivity for the detection of high and low glucose; however, the frequent false alarms can be a source of irritation and disrupt sleep, leading to *alarm fatigue* in some individuals, with a related tendency to ignore the alarms. There is also a risk of people sleeping through alarms. Buckingham et al. [35] found that people who were videotaped while sleeping awoke to only 29% of individual alarms and 66% of repeated alarms.

The adjustment of alarm thresholds is a stepwise process by first deciding on initial thresholds when initiating use of the sensor, and then optimizing alarm thresholds over time based on retrospective review of continuous glucose tracings. For those with hypoglycaemia unawareness or a history of severe hypoglycaemic reactions, where the overriding imperative is on reducing hypoglycaemia, the low glucose alarm threshold should be set at 4.5 mmol/l (80 mg/dl) or higher. However, the physiological lag between blood and interstitial glucose when the sensor alarm is triggered also depends on the device.

For individuals without a history of problematic hypoglycaemia, it is common practice to set the initial glucose thresholds at 3.0–3.5 mmol/l (55–60 mg/dl) and ≥14 mmol/l (250 mg/dl). This ensures that during the initial period after starting the use of CGM, while the individual is mastering the use of the technology, there will be fewer intrusive and irritating alarms, and less risk of alarm burnout. Over time, as the individual uses the information from the sensor to reduce glucose excursions, the alarm settings can be brought closer to target glucose levels, and this can assist with further improvement of glycaemic levels. Alarm messages and trend arrows of the CGM devices allow a near-normal, *tighter*, and safer adjustment and, through the trend arrows, targeted, forward-looking therapy adjustments.

Skin issues with continuous glucose monitoring

Wearing glucose sensors on the skin for 14 days and repeated use of the same skin site can lead to skin reactions in these areas. The reactions range from mild skin irritations to the development of contact allergies in some people with diabetes. Eczematous reactions to pump and CGM devices represent the most common skin complications [36]. This underscores the need for regular skin examination as an integral part of the diabetes consultation and for interdisciplinary collaboration on classification and treatment options. Currently, many papers are published showing allergic contact dermatitis to device patches [37]. The allergic reaction not only leads to immediate symptoms, but can make the further use of this CGM system impossible and can lead to accompanying reactions to the plasters when using other technical systems (e.g. an insulin pump). Manufacturers of future medical devices will need to pay attention to the tolerability as well as durability of the patches. The substance isobornyl acrylate (IBOA) [38] has now been identified as a cause of contact dermatitis and is currently the subject of further investigation [39, 40]. The work from our clinic could show that despite device-associated skin reactions, the quality of life of the users is mostly not limited [36].

Skin care is of particular importance. For the removal of sensor, catheter, and patch residues, products that work on the basis of saturated hydrocarbons, alcohol, silicone, or oil can be used exactly according to instructions. If irritation is visible, skin protection products that leave a protective film or barrier between the skin and the adhesive of the patch can be used. For example, hydrocolloid-based plasters, which actually serve a different purpose and are used in ostomy care, can be helpful here [41]. They have very good skin compatibility and often maintain the protective skin barrier for the entire time the sensor is worn. In order to improve the adhesion properties, a protective film can be used. Most sensors can be simply taped over without pressure. A small piece of swab or tissue will prevent the foil from sticking to the transmitter or sensor. In particular, when bathing or visiting the swimming pool, a waterproof cover should be applied. Removing the waterproof foil is not necessary, but the adhesive quite often causes skin redness. In severe cases, even this may no longer be sufficient. Alternatives that do not contain IBOA are recommended, like the implantable Eversense system [42].

Use of capillary blood glucose monitoring and continuous glucose monitoring to guide management and assess outcomes

There are various ways beyond HbA_{1c} in which glucose data can be used for daily diabetes management decision making and during clinical trials. Over time these are evolving from seven-point capillary blood glucose monitoring [43] and the display of a typical CGM profile [44] to the ambulatory glucose profile (AGP) with trends [45] and glycaemic patterns [46] (Figure 32.6).

Visualization, analysis, and documentation of key capillary blood glucose monitoring metrics

In order to achieve therapy goals (e.g. an HbA_{1c} value set with the diabetes team, reduction of hypoglycaemia, improvement of prepprandial or post-prandial glucose values), people with diabetes regularly measure the glucose concentration in capillary blood samples to monitor the glucose trend. Blood glucose measurements are also used to detect acute metabolic disorders (hypoglycaemia or hyperglycaemia). Capillary blood glucose data may be used in various ways. With multiple daily insulin therapy, individual values are used to determine the next dose of insulin and to teach people with diabetes the effects of specific foods, exercise, and other activities on blood glucose levels. For people with diabetes on all types of therapy, capillary blood glucose data may be used by the physician to guide treatment decisions based on the overall pattern of results.

Because of the large volume of data that may be generated, and the often haphazard record keeping, recognizing glycaemic patterns may be difficult. For this reason, there has been a move to incorporate new technology to simplify this task and make it more accurate.

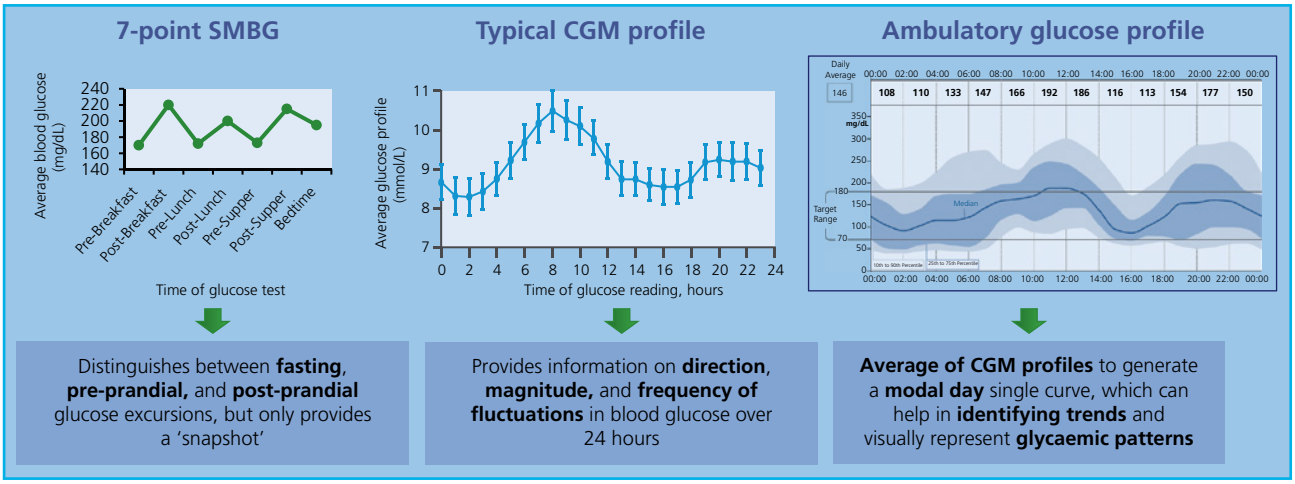


Figure 32.6 Comparison of data visualization with capillary blood glucose monitoring or continuous glucose monitoring (CGM) and the ambulatory glucose profile. SMBG, self-monitored blood glucose.

Such developments have come from manufacturers of glucose measuring systems, from suppliers of mobile phones and other telemedicine systems, and from various start-up companies. Systems have also been designed to produce graphical results of glucose patterns and have been shown to improve glycaemic management. The graphical output can be either on the meter itself [47] or using software that downloads capillary blood glucose data from the meter [48].

Assessment of glucose variability

A major limitation of HbA_{1c} is that it does not provide any information about the timing and magnitude of glucose variability, nor does it give data regarding the timing and frequency of hypoglycaemia [49]. However, from a clinical point of view, glycaemic variability is of relevance with respect to acute and long-term treatment of people with diabetes and is a consistent predictor of hypoglycaemia, both in prospective studies and within the setting of randomized clinical trials [50]. Relationships between increased glucose variability and many other outcomes, including microvascular and macrovascular outcomes, have been less consistent.

Standard deviation (SD) and coefficient of variation (CV) are widely used to quantify glucose variability [49]. The CV has the advantage of being a metric relative to the mean, which makes it more descriptive of hypoglycaemic excursions than the SD alone. In addition to these standard statistics, various diabetes-specific metrics of glucose variability have been introduced during the last half-century (reviewed in [49]), beginning with the M-value based on a logarithmic transformation of the glucose deviation from a pre-set value (e.g. 120 mg/dl [6.7 mmol/l]). Among these metrics, mean amplitude of glucose excursions (MAGE) has been one of the most widely used. The mean of daily differences (MODD) was introduced as a measure of inter-day variability, and the continuous overlapping net glycaemic action (CONGA) was presented as a composite index of the magnitude and the timing of glucose fluctuations captured over various time periods.

Several metrics based on this risk function of glucose variability have been introduced: the low glucose index (LGI) increases with the frequency and extent of hypoglycaemic excursions and, by design, ignores hyperglycaemia; the high glucose index (HGI) increases with the frequency and extent of hyperglycaemic excursions and ignores hypoglycaemia; and the average daily risk range (ADRR) is equally sensitive to both low and high glucose excursions. The LGI is predictive of severe hypoglycaemia, the HGI is associated with HbA_{1c} and hyperglycaemic excursions, and the ADRR is a measure of overall glucose variability that captures the risk of both hypoglycaemia and hyperglycaemia. The lability index and the mean absolute glucose change (MAG) have been introduced and used in hospital settings to assess the effects of islet transplantation or increased risk for mortality in intensive care.

A more standard approach was used to define the threshold for excess glucose variability; here, the CV is preferred over the SD because it is independent of the mean glucose concentration. A % CV of 36% appears to be a suitable threshold [51] to distinguish between stable and unstable glycaemia in diabetes, because above this limit the frequency of hypoglycaemia is significantly increased, especially in people treated with insulin [51].

Statistical methods available for the analysis of CGM data include graphs, such as a Poincaré plot of system stability, and variability-grid analysis (VGA), used to visualize the glycaemic fluctuations captured by CGM. VGA was also used to depict the efficacy of closed-loop control algorithms [52]. Because the more comprehensive statistical assessments (e.g. Poincaré plot) would be reserved for in-depth scientific analysis of data, it is recommended that if the intent is to assess the effects independent of mean glucose, CV may be best and preferred over SD [13].

Time in range

Time in range (TIR), defined as the time during which glucose is within a predefined target corridor, was developed on the basis of data available from rtCGM or isCGM for both short- and longer-term glycaemic management. For the assessment of CGM results, the Advanced Technologies & Treatment for Diabetes (ATTD) Consensus defined a range of 70–180 mg/dl (3.9–10.0 mmol/l) as a target corridor [13], above which there is an increasing risk of hyperglycaemia and thus also of diabetic ketoacidosis, or below which there is an increased risk of hypoglycaemia [53]. The relative time within this target corridor (as a percentage or, alternatively, as hours per day) was defined in this context as TIR. As a general trend, the lower the TIR, the higher is the glucose variability and the higher the risk of hypo- and hyperglycaemic complications [54]. Furthermore, several studies show (not without exception [49]) an association between increased glucose variability (or low TIR) and

diabetes-associated complications such as retinopathy, microalbuminuria, and neuropathies [55–57]. TIR is now also used to evaluate new pharmacological diabetes therapies [58] and is considered by the FDA to be an appropriate endpoint to determine how successfully an artificial pancreas can maintain glucose within a predefined target range [58, 59]. In meta-analyses of different *closed-loop* approaches, TIR offers the possibility of comparison between individual studies and technical alternatives [56].

Practicalities for evaluating CGM data and targets for TIR have been agreed in three consensus meetings [4, 13, 58]. The *target range* for TIR is defined as 70–180 mg/dl (or 3.9–10.0 mmol/l) (Table 32.4). Hypoglycaemia values between 54 and 70 mg/dl (3.0–3.9 mmol/l) are classified as relevant hypoglycaemia (level 1) and those <54 mg/dl (<3.0 mmol/l) are classified as serious, clinically relevant hypoglycaemia (level 2). Respectively, for hyperglycaemia: values >250 mg/dl (>13.9 mmol/l) are defined as serious hyperglycaemia (level 2) and values between 181 and 250 mg/dl (10.1–13.9 mmol/l) as relevant hyperglycaemia (level 1). In the case of severe hyperglycaemia, additional ketone bodies should be determined in the blood or urine under certain conditions to detect impending ketoacidosis in good time. Individual target values closer to the physiological normal range could be defined depending on the person's age, concomitant diseases, or engagement with self-management. Nocturnal glucose control is defined as the period between midnight and 6 a.m. For clinical trials, it is recommended that TIR and coefficients of variation be reported separately for night (midnight to 6 a.m.), day (6 a.m. to midnight), and 24-hour periods.

Establishing target *percentages* of time in the various glycaemic ranges with the ability to adjust the percentage cut points to address the specific needs of special diabetes populations (e.g. pregnancy, high risk) would facilitate safe and effective therapeutic decision making within the parameters of the established glycaemic goals (Table 32.4).

The composite metric includes three key CGM measurements: percentage of time per day within target glucose range (TIR), time below target glucose range (TBR), and time above target glucose range (TAR) (Figure 32.7). The primary goal for effective and safe

Table 32.4 Guidance on targets for assessment of glycaemic indices for those with type 1 diabetes or type 2 diabetes and older and high-risk individuals [5]

	Time in Range (TIR)		Time Below Range (TBR)		Time Above Range (TAR)	
Diabetes group	**Target Range**	**% of readings time/day**	**Below Target Level**	**% of readings time/day**	**Above Target Level**	**% of readings time/day**
Type 1 diabetes*/ type 2 diabetes	70–180 mg/dl 3.9–10.0 mmol/l	**>70 %** **>16h, 48 min**	<70 mg/dl <3.9 mmol/l <54 mg/dl <3.0 mmol/l	**<4 %** **<1 h** **<1 %** **<15 min**	>180 mg/dl >10.0 mmol/l >250 mg/dl >13.9 mmol/l	**<25 %** **<6 h** **<5 %** **<1 h, 12 min**
Older/high-risk#						
Type 1 diabetes / type 2 diabetes	70–180 mg/dl 3.9–10 mmol/l	**>50 %** **>12 h**	<70 mg/dl <3.9 mmol/l	**<1 %** **<15 min**	>250 mg/dl >13.9 mmol/l	**<10 %** **<2 h, 24 min**

Each incremental 5 % increase in TIR is associated with clinically significant benefits
14 days with at least 70 % of data recommended for evaluation
* For age <25 years, if the HbA_{1c} goal is 7.5 % (58 mmol/mol) then set TIR target to approximately 60 %.
# it is important to individualize and be conservative, with a strong focus on reducing the percentage of time spent <70 mg/dl (<3.9 mmol/l) and preventing excessive hyperglycaemia.

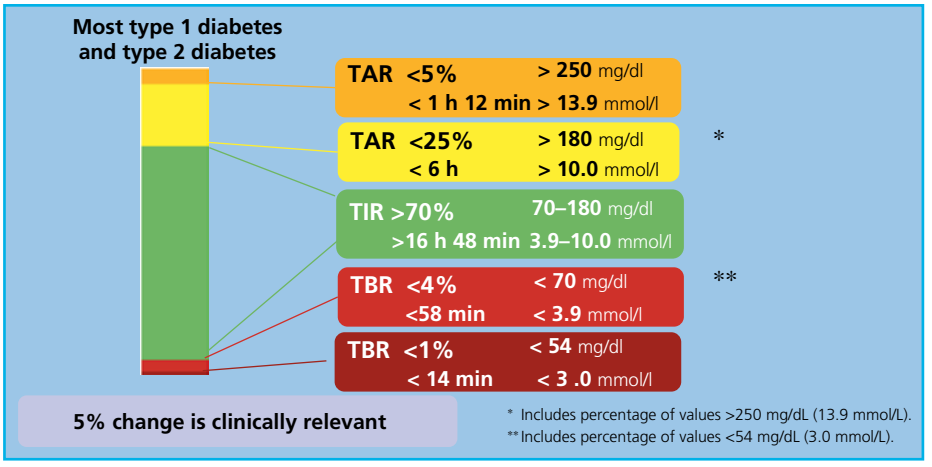


Figure 32.7 The 2019 Advanced Technologies & Treatment for Diabetes (ATTD) Consensus for continuous glucose monitoring time in range (TIR) targets for most individuals with type 1 diabetes and type 2 diabetes. TAR, time above target glucose range; TBR, time below target glucose range. Source: Modified from Battelino et al. 2019 [4].

glucose management is to increase the TIR while reducing the TBR. Expressing time in the various ranges can be done as the percentage (%) of CGM, average hours and minutes spent in each range, or both, depending on the circumstances (Table 32.4). Targets have been proposed for most individuals with type 1 diabetes and type 2 diabetes, including children and distinct targets for those at high risk (for example, hypoglycaemia unawareness) or frail and older people. Also, women with type 1 diabetes or type 2 diabetes during pregnancy and those with gestational diabetes should strive to achieve separate goals [4]. In any case, the first priority is to reduce TBR to target levels and then address TIR or TAR targets.

For people with type 1 diabetes, the targets are informed by the ability to reach the targets with hybrid closed-loop therapy [59–63]. Importantly, recent studies have shown the potential of reaching these targets with CGM in individuals using multiple daily injections [64]. In type 2 diabetes, there is generally less glycaemic variability and hypoglycaemia than in type 1 diabetes [65]. Thus, people with type 2 diabetes can often achieve more time in the target range while minimizing hypoglycaemia [66]. A novel single-number summary of the quality of glycaemia is the Glycemia Risk Index (GRI) [67].

Ambulatory glucose profile

To establish TIR as a clinical standard, Bergenstal et al. developed an ambulatory glucose profile (AGP) for interstitial glucose monitoring systems that indicates TIR itself, but also shows pattern recognition [68]. The more advanced rtCGM or isCGM devices have higher accuracy in glucose measurement and effective algorithms for converting the sensor measurement signal to the displayed glucose value compared with the past [69]. In addition, the values and the decision criteria relevant to the person with diabetes are now displayed in a more patient-friendly manner. An example of the practical implementation of this method is shown in Figure 32.8 and demonstrates clarity and good manageability in the daily routine of people with diabetes; it can also be used without extensive laboratory diagnostics, in contrast to a measured HbA_{1c}. Visualization makes it easier for people with diabetes to use on a daily basis, and the effects of meals, exercise, medications, or changes in treatment regimen can be shown. This increases the understanding of phases of relative hypo- and hyperglycaemia and consequently these can be reduced.

Each manufacturer offers its own software for evaluating CGM data. The software programs can be complex and require an introduction. Current software usually offers a clear initial evaluation of CGM data using the AGP to calculate CGM-derived parameters such as mean glucose, glucose management indicator (GMI) [70], glycaemic variability, or time in, above, or below target range (TIR, TAR, TBR). The presentation as a clear graph also enables a quick overview. In the AGP, the median glucose progression is displayed from the measured values of several days. This shows the mean glucose curve at each point in time of the standard day. The graph identifies two other major glucose ranges. The blue area surrounding the median curve is the interquartile range (IQR), where 50% of all measured glucose values lie. The wider area is the interdecile range (IDR), which is bounded by the 10th and 90th percentiles. This is where 80% of the readings lie. The width of the IQR and IDR shows how much the measured values scatter; in other words, the glucose variability. The physician and diabetes team can therefore see at a glance the individual's median glucose over 24 hours and the glucose variability.

In addition, the AGP provides information on other important parameters, such as the median glucose value and areas of high and low glucose values. Hypoglycaemic events can be analysed accurately, as their number, duration, depth, and frequency in the selected period are determined with most of the current software solutions. It also provides the person with diabetes with an easy-to-understand picture of their glucose profile. Diabetes communities often discuss the AGP on social media to find therapeutic measures that help to achieve a flat, narrow, and in range (FNIR) day (Figure 32.9).

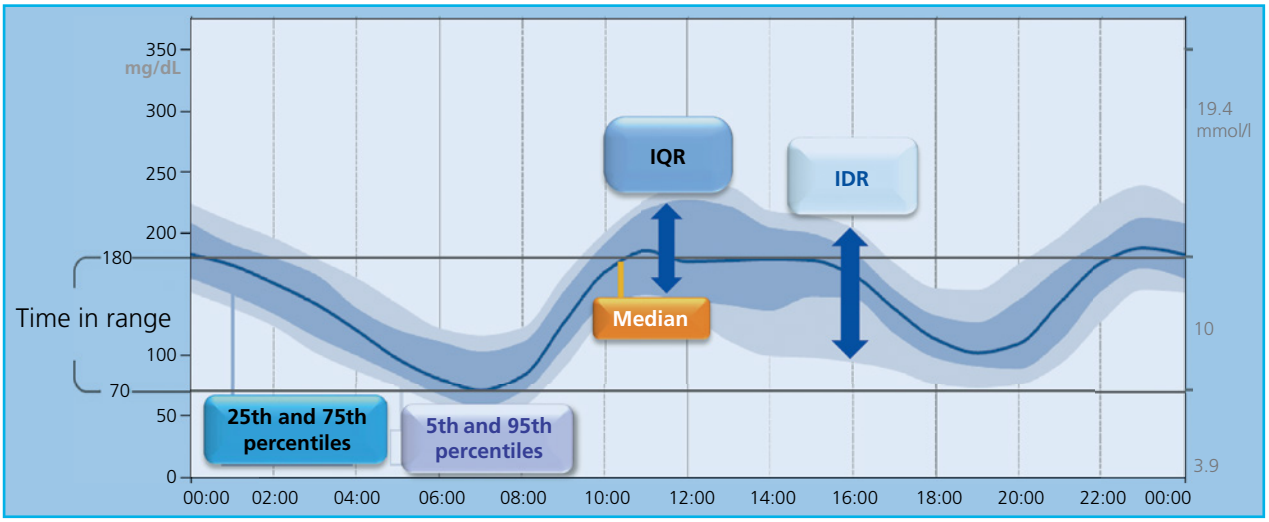


Figure 32.8 Interpreting glucose variability with the ambulatory glucose profile (AGP). If there is variability of glucose values in the interquartile range (IQR: blue area), then adjust the therapeutic regimen. If variability is predominantly in the interdecile range (IDR), then discuss potential lifestyle changes during the individual consultation. High glucose variability is associated with increased risk for hypoglycaemia.

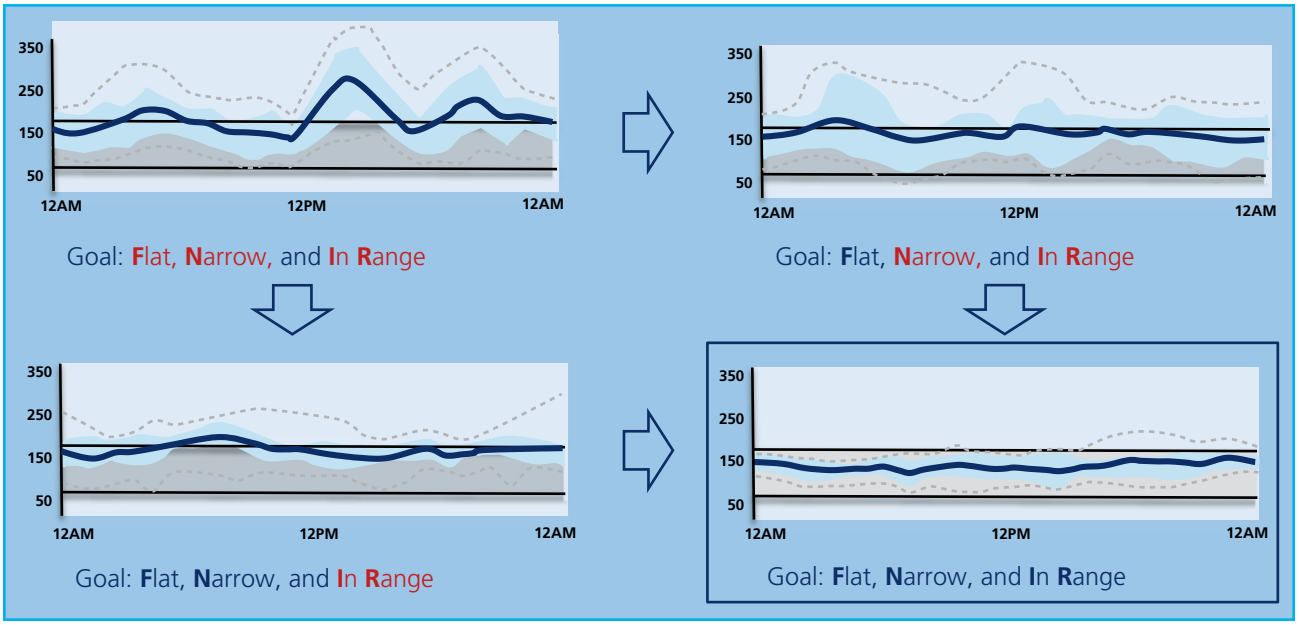


Figure 32.9 There are various ways in which continuous glucose data can be used to inform successful adjustments of the therapeutic regimen. Flat, narrow, and in range (FNIR) is one way to think about *ideal* blood glucose levels: high time in range and flat glucose levels with few ups and downs. People with type 1 diabetes or type 2 diabetes can strive for FNIR. On a day with FNIR levels, people should be encouraged to ask: What made that possible? How can I have more days like that? (See https://diatribe.org for details.)

The information displayed in the recommended AGP report can be used to analyse the AGP in a structured manner (Figure 32.10) [13, 66]. Experts recommend a five-step approach (Box 32.3) [71].

Future perspectives for continuous glucose monitoring

Transition from capillary blood glucose monitoring to continuous glucose monitoring

The performance of capillary blood glucose monitoring systems has improved in recent decades to such an extent that considerable further improvements are no longer expected in the foreseeable future. Capillary blood glucose monitoring still has the largest market share of glucose monitoring systems in the field of diabetes technology, partly due to the lower costs compared to rtCGM/isCGM systems. Continuous measurement systems such as rtCGM and isCGM are gaining in acceptance and importance, however. One important option for further development of all devices for glucose monitoring is their interoperability; that is, improved automatic availability of measurement results for evaluating data in programs or apps. As long as CGM is still costly and difficult to wear for individuals, these devices may be used intermittently and for a limited time, especially in cases of limited resources. From a global perspective, intermittent CGM use is more likely to occur than continuous use, primarily for economic reasons [72].

In the future, the merging of data, including those from the insulin dose (by using smart pens), carbohydrates (by an automated analysis of the carbohydrate content of meals), or exercise (by using data from fitness wristbands), will enable calculation of the optimal insulin dose thanks to the possibility of analysing data from many sources. Future bolus calculators will process such data and thus relieve people with diabetes of error-prone calculations.

Using continuous glucose monitoring in the virtual diabetes clinic

The virtual diabetes clinic has been a goal of healthcare systems and expert diabetes professionals for some time. Based around the growing number of diabetes-enabling technologies, telemedicine has been proposed as an important solution to the need to expand care for the benefit of people with diabetes, while improving efficiencies and rationalizing costs [73]. Telemedicine with CGM has been transformed from an aspirational goal to become the *de facto* standard of care for diabetes management during the Covid-19 public health emergency. Virtual consultation using continuous glucose data has been an invaluable tool in glycaemic management for a significant subset of those able to access this technology, most evidently for people with type 1 diabetes. Telemedicine is an acknowledged part of the post–Covid-19 world, but telemonitoring via CGM is still possible only for a subset of people with diabetes.

The diabetes services adapting most quickly to the needs of people with diabetes appear to be those with the most experience and confidence of working with diabetes health technologies and creating their own diabetes health ecosystems. These are often paediatric services. Given the mounting shortage of endocrinologists, especially in rural areas, the current paradigm of clinical care lacks the ability to provide the timely insulin adjustments needed to improve the management of type 1 diabetes. Digital decision support systems can address these issues by facilitating timely and more frequent insulin dose adjustments, either in person or remotely. Frequent insulin dose adjustments guided by an automated, artificial intelligence–based decision support system were as effective and safe as those guided by physicians in controlling glucose levels. In a six-month, multicentre, multinational, parallel, randomized controlled non-inferiority trial of 108 participants with type 1 diabetes, aged 10–21 years and using insulin pump therapy, use of an automated decision support tool for optimizing insulin pump settings was

AGP Report

Name

MRN

GLUCOSE STATISTICS AND TARGETS

26 Feb 2019–10 Mar 2019	**13 days**
% Time CGM is Active	**99.9%**

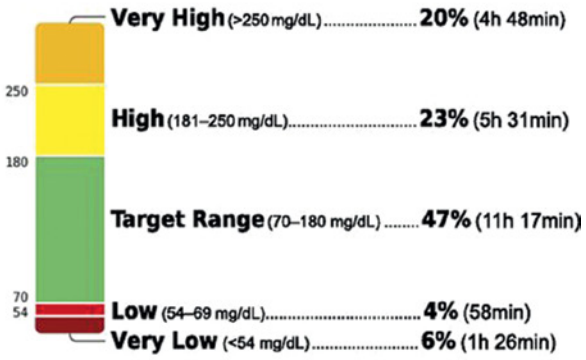
Glucose Ranges	**Targets** [% of Readings (Time/Day)]
Target Range 70–180 mg/dL	Greater than 70% (16h 48min)
Below 70 mg/dL	Less than 4% (58min)
Below 54 mg/dL	Less than 1% (14min)
Above 180 mg/dL	Less than 25% (6h)
Above 250 mg/dL	Less than 5% (1h 12min)

Each 5% increase in time in range (70–180 mg/dL) is clinically beneficial.

Average Glucose	**173 mg/dL**
Glucose Management Indicator (GMI)	**7.6%**
Glucose Variability	**49.5%**

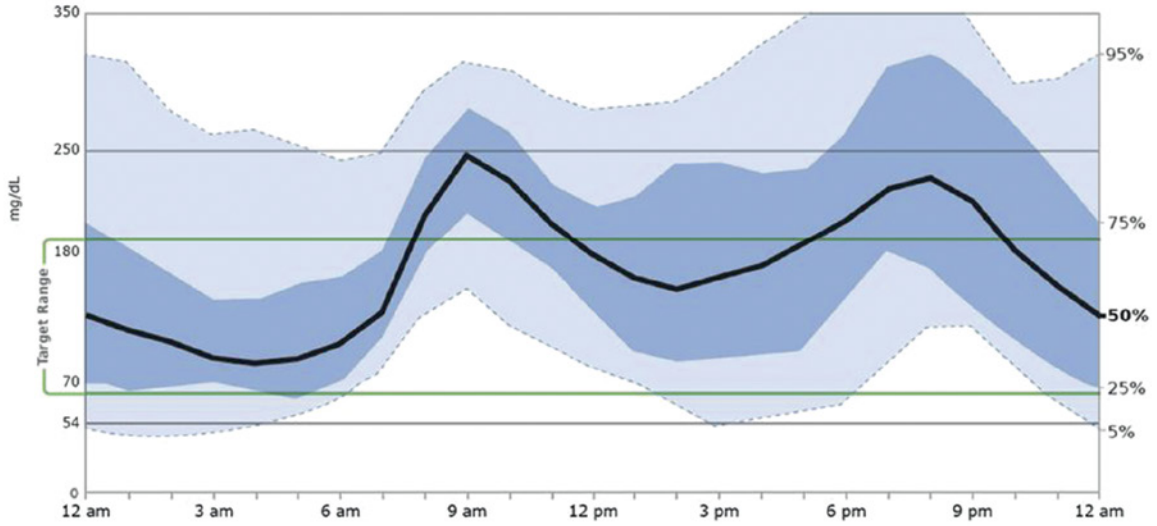
Defined as percent coefficient of variation (%CV); target ≤36%

TIME IN RANGES

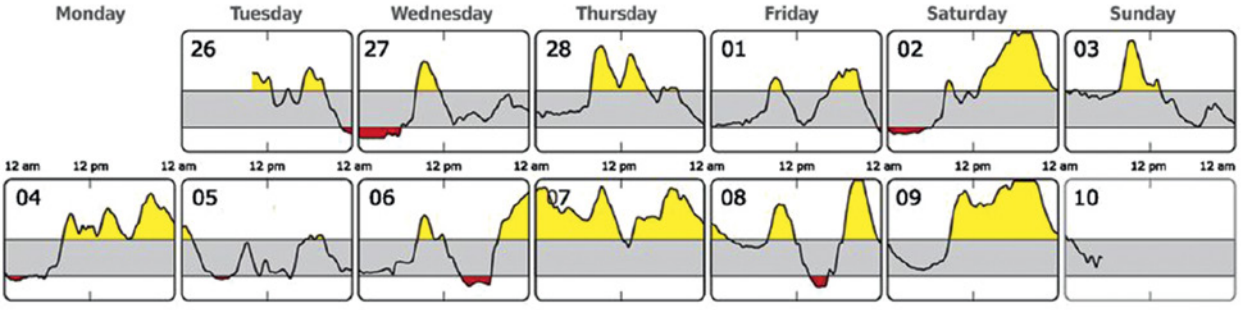


AMBULATORY GLUCOSE PROFILE (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if occurring in a single day.



DAILY GLUCOSE PROFILES



Each daily profile represents a midnight-to-midnight period.

Figure 32.10 The structured ambulatory glucose profile (AGP) report as suggested by the consensus group. Source: Modified from Battelino et al. 2019 [4].

Box 32.3 Stepwise structured analysis of the ambulatory glucose profile

1. What are the data quality and quantity?
The quality and quantity of the data are essential to the interpretation of the ambulatory glucose profile (AGP). An evaluation period of at least 14, but not more than 28, days is optimal to make a relevant statement about patterns. A period with standard conditions should be selected to inform therapeutic decisions. Vacations and illness, for example, are exceptions to the daily routine, during which glucose values may be different despite the same insulin dose. Using the measurement sensor for more than 70% of the evaluation time is considered sufficient. Data gaps can reduce the significance of the analysis.

2. What are the target range and time in the target range?
Usually a target range of 70–180 mg/dl (3.9–10.0 mmol/l) is recommended. A tighter range (70–140 mg/dl; 3.9–7.8 mmol/l) can be used in those striving for normoglycaemia.

3. Does the person with diabetes have hypoglycaemia?
In general, preventing hypoglycaemia, and especially severe hypoglycaemia, is one of the primary goals of therapy adjustment. To analyse hypoglycaemia, it is advisable to check individual days in addition to pattern recognition in the AGP.

4. What is the glucose variability?
The fourth step of the analysis is to evaluate glucose variability. This will reveal variations typical of the time of day and allow specific therapy adjustments. Glucose variability can be differentiated using interquartile range (IQR) and interdecile range (IDR). A broadened IQR usually indicates that changes in the therapeutic regimen are needed. In contrast, issues related to a wide IDR are more likely to be caused by lifestyle issues of the individual, such as an irregular daily routine or skipping or reducing a mealtime bolus. However, irregular daily routines eventually contribute to both a wider IDR and a wider IQR. For an in-depth analysis, additional information such as the amount and time of intake of carbohydrates and insulin, as well as information on exercise or illness, should be recorded.

5. What about the stability of the glucose profile?
This refers to the example of being flat, narrow, and in range (FNIR) described in Figure 32.9. Steep rises and falls indicate a need for optimization. Possibly the coefficient of variation (CV) can be used in addition. A CV >36% signifies instability with an increased probability of hypoglycaemia. As a general rule, if the analysis shows that therapy adjustments are needed, do not address too many issues at once.

non-inferior to intensive insulin titration provided by physicians from specialized academic diabetes centres [74].

Using continuous glucose monitoring for automated insulin dosing

A sophisticated artificial pancreas would be a device that mimics the glucose-regulating functions of a healthy pancreas, automatically controls blood glucose levels without patient intervention, and delivers insulin. Previous attempts to perform fully automatic insulin therapy (e.g. without meal announcement) using a control algorithm have not been successful.

Post-prandial hyperglycaemia is a particular problem here, since a fully automated system based on a glucose sensor alone can only respond to increases in glucose. However, this response first needs a certain glucose gradient for a rise to be detected as a meal [75]. The subsequent insulin release thus follows an already incipient hyperglycaemia, which is further intensified because even with new, ultra-short-acting insulins, the pharmacodynamic onset of action occurs after ~10 minutes.

However, it can be assumed that the current treatment standard of intensified insulin therapy with syringes, pens, or insulin pumps will increasingly be supplemented by systems for automatic insulin dosing based on CGM using smart pens or so-called hybrid closed-loop systems. As can be seen in other technologies like mobile phones, more diverse and advanced hybrid close-loop systems will continually come onto the market. They are characterized by automatic corrections of bolus delivery and basal rate, but a meal input remains necessary. However, they differ considerably both in the underlying algorithm and in the target values, sports, or sleep settings. This form of therapy requires trust in the system, as its use is associated with a transfer of tasks and responsibility. Since the people with diabetes and parents of children with diabetes have to modify the learned principles of diabetes therapy, good, detailed, and repetitive structured training of people with diabetes is still necessary. A life that should differ as little as possible from that of those without diabetes is the goal.

It is likely that only a few diabetes teams will fully master the advantages and disadvantages of the different systems for AID to provide informed advice to people with diabetes and to identify the most suitable system for each individual during the consultation. One of the challenges of the future will be to find a basis for adequate system selection, training, and reimbursement of the next generation of diabetes therapy.

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33 New Technologies for Insulin Administration

Hannah Forde and Pratik Choudhary
Leicester Diabetes Centre, Leicester, UK

Key points

- The emergence of new technologies for insulin delivery as well as glucose monitoring has led to significant improvements in the care of type 1 diabetes.
- Insulin pen technology has significantly advanced since the first pen was launched by Novo Nordisk in 1985 and now 'smart' connected pens are available, which can record the timing and dose of insulin administration and communicate with blood glucose monitoring and continuous glucose monitoring (CGM) systems.
- Several 'smart' insulin pen products (caps and attachments) are also in production that will integrate with various insulin pens to track insulin dosage and timing.
- Newer insulin pumps are smaller, more portable, and user friendly and have greater technological capabilities, including temporary basal rates/patterns, advanced bolus options, bolus advisors, and the ability to integrate with CGM.
- There is conflicting evidence on whether continuous subcutaneous insulin infusion (CSII) therapy is superior to multiple daily injections for achieving optimum glycaemic levels and reducing hypoglycaemia. However, people with elevated glycated haemoglobin (HbA_{1c}) or a high burden of hypoglycaemia seem to gain the most benefit from pump therapy.
- Data from both randomized controlled trials and observational studies confirm a positive effect of CSII on the quality of life of people with type 1 diabetes.
- Tubeless 'patch' pumps are now available and these may have some advantages over conventional 'tubed' pumps, though there are limited data comparing the two types of device.
- The most common insulin pump–associated adverse effects are related to problems with infusion sets.
- Intraperitoneal pumps remain a valuable option for those in whom subcutaneous insulin therapy fails.
- Glucose-responsive smart insulin delivery systems are currently in development and represent a promising area of research.

Insulin therapy has evolved since its discovery 100 years ago, and insulin analogues have more or less replaced the traditional basal-bolus regimens of human insulins and neutral protamine Hagedorn (NPH). Insulin analogues are associated with improved glycaemic levels, less day-to-day variability, and reduced hypoglycaemia in people with type 1 diabetes, compared to human insulin preparations whose pharmacodynamic properties result in large fluctuations in the glycaemic profile [1]. Although basal-bolus regimens with newer insulins have significantly improved type 1 diabetes care, the quest for more physiological insulin delivery is ongoing.

As the insulins themselves have progressed, so too have their delivery systems. Conventional insulin administration involved subcutaneous injections with syringes marked in insulin units. Depending on the manufacturer, traditional syringes differed in gauge, capacity, and needle length [2]. This was the only mode of insulin delivery available for decades and made the process of giving an insulin injection impractical, time-consuming, and socially unacceptable for many people living with diabetes. Syringes have now been superseded by insulin pen devices, which are recognized as being easier to use, more convenient, and less painful, while providing greater dose accuracy and increased life flexibility [3, 4].

Another mode of insulin delivery is the insulin pump or continuous subcutaneous insulin infusion (CSII). CSII uses a portable, battery-operated programmable pump to continuously infuse rapid-acting insulin at a slow and variable basal rate over 24 hours, with additional bolus insulin administration directed by the user when food is eaten or to correct hyperglycaemia [5]. CSII offers increased flexibility for people with type 1 diabetes and may be considered superior to multiple daily injection (MDI) for some individuals with diabetes.

The emergence of new technologies for insulin delivery as well as glucose monitoring has led to significant improvements in type 1 diabetes care. Efforts are ongoing to identify new minimally invasive methods of insulin administration that are safe, effective, and will further reduce the burden of living with diabetes. In this chapter, we discuss a range of new technologies for insulin delivery and review the available evidence investigating their use in clinical practice.

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Insulin pens

The first insulin pen, NovoPen®, was manufactured in 1985 by Novo Nordisk (Bagsværd, Denmark) [6]. Insulin pens were designed to alleviate many of the limitations of vials and syringes. Indeed, the advantages of insulin pens over syringes have been proven in many studies [7–10]. Since then several disposable or reusable, pre-filled or refillable insulin pen devices have been developed, which can deliver long-acting, rapid-acting, and mixed insulins. More recently, insulin pen devices have been further refined and many now include advanced 'smart' features to address problems such as hypoglycaemia, medication taking, insulin initiation, and titration and dosing errors [11].

In 2017, the first US Food and Drug Administration (FDA)–approved insulin smart pen was released [12]. The InPen® system, manufactured by Companion Medical (San Diego, CA, USA), records the amount and timing of the insulin dose and transmits the information via Bluetooth to a smartphone app. It can be used with either insulin aspart (NovoLog®/NovoRapid®, Novo Nordisk) or insulin lispro (Humalog®, Eli Lily, Indianapolis, IN, USA) [13]. The dedicated smartphone app includes a bolus calculator, which adjusts the insulin dose recommendation for insulin on board (IOB). The app can also prepare reports that can be shared with healthcare professionals, to assist in identifying trends to inform treatment decisions. There are numerous other smart insulin pens, which can precisely track insulin delivery and wirelessly transmit the data to a smartphone app, but these do not have the additional advantage of a bolus calculator.

Novo Nordisk has also contributed to the smart pen market. The NovoPen®5 and NovoPen® Echo devices were its first smart pens for adults and children, respectively. These devices, compatible with insulin aspart, have a built-in memory function that records the last dose in units as well as the time elapsed since the last injection. The information is displayed electronically on the pen and there is an additional safety feature that clicks when the full dose of insulin has been administered [14]. Novo Nordisk has also recently launched *smart connected pens*, the Novopen®6 and NovoPen Echo® Plus. These pens communicate with continuous glucose monitoring (CGM) systems and blood glucose meters, and Novo Nordisk has established partnerships with several glucose monitoring companies to allow integration of glucose monitoring and insulin dosing data. The effect of a smart connected insulin pen on glycaemic management was investigated in a non-interventional study in a Swedish cohort of almost 100 adults with type 1 diabetes [15]. In this study, the participants received the Novopen®6 device and CGM was utilized to monitor *time in range* (TIR) and hyper- and hypoglycaemia [15]. The device was associated with a significant increase in TIR and a significant reduction in hyper- and mild hypoglycaemia (3.0–3.9 mmol/l) [15]. It is worth noting, however, that there was no control arm in this study and the individuals with diabetes had frequent visits with healthcare professionals (>5 visits in a period of six months), which may have accounted for some of the improvement in glycaemic levels [15].

Several insulin pen products, including smart caps and attachments that can integrate with different insulin pens, are in various stages of development and commercialization, offering the ability to passively track insulin doses and timing and allowing varying degrees of integration with electronic health records and glucose monitoring platforms [16]. Some attachments interface with a smartphone app and have alert features to avoid missed or extra doses of insulin. Unintentional omission of insulin is common; in a telephone survey of more than 500 persons with diabetes, 7.4% of respondents chose *forgot* when selecting their top three reasons for omitting insulin [17]. Forgetting, or questioning an insulin dose, affects insulin-taking behaviour and increases worry and concern for individuals with type 1 diabetes [18]. Smart caps and attachments are novel strategies that can assist people with type 1 diabetes in the management of memory-related dosing issues. The efficacy of the InsulClock® (InsulCloud, Madrid, Spain) was assessed in a single-centre pilot study in 16 people with suboptimally managed type 1 diabetes [19]. The device shows type, time, and quantity of insulin administered and interfaces with an app that provides dose reminders and allows food/glucose data input [14]. In this small study, InsulClock use was associated with increased TIR and reduced hyperglycaemia, coupled with improved insulin administration and treatment satisfaction [19].

These devices are also useful research tools. The Gocap (Common Sensing, Cambridge, MA, USA), which interfaces with an app and displays the type and time of insulin administration and allows for relevant data entry, has been used to objectively evaluate insulin administration in 75 individuals using an MDI regimen [20]. With the use of this Bluetooth-enabled pen cap, the study identified that 24% of bolus doses and 36% of basal doses were dosed or timed inaccurately [20]. Additionally, the Gocap has been used in conjunction with CGM to illustrate the effect of insulin dose and timing on post-prandial glucose readings [21]. Access to these data could facilitate healthcare professionals and people with type 1 diabetes to make effective changes to their bolus insulin regimen.

i-Port

Injection ports are a viable alternative to subcutaneous insulin injections [22]. The i-Port Advance™ (Medtronic, Minneapolis, MN, USA; Figure 33.1) is a small injection port that allows the person with diabetes to take multiple daily subcutaneous injections without having to puncture the skin each time [22]. It can be worn for up to three days during all normal daily activities. Khan and Alswat assessed the impact of the i-Port Advance on satisfaction, insulin administration, and treatment outcomes in 55 people with insulin-treated diabetes (92.7% type 1 diabetes) [23]. They reported

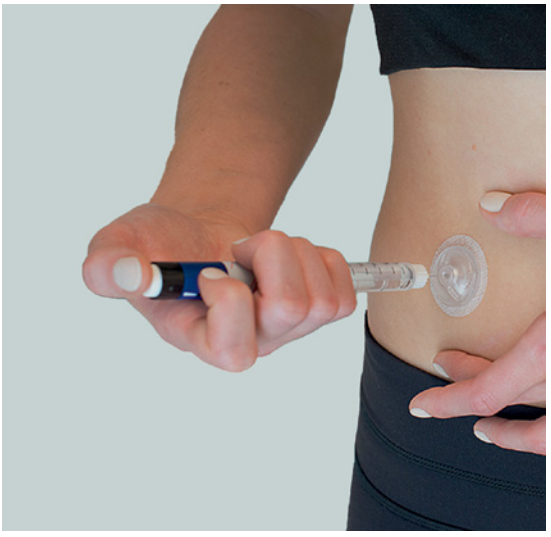

Figure 33.1 The i-Port Advance™ system. Source: With permission from Medtronic.

improved insulin administration and reduced frequency of hypoglycaemia and hospitalizations with the i-Port, but there was no significant difference in glycaemic levels or treatment satisfaction among regular and irregular users of the system [23]. Gregory et al. described another potential use of the i-Port system when it was used effectively to desensitize an individual with type 1 diabetes complicated by insulin allergy to subcutaneous insulin [24]. While i-Ports may be useful for those with severe needle phobias, their use has not been widely adopted in clinical practice. This is likely due to the availability of newer and smaller needles, which make insulin injections almost painless [23].

Continuous subcutaneous insulin infusion

The first use of CSII with an insulin pump was described in 1978 by Pickup et al. in 12 individuals with 'insulin-dependent' diabetes [25]. Though there was initial excitement surrounding CSII therapy, pumps soon fell out of favour as concerns grew over their size, safety, and efficacy [26]. A strong resurgence occurred following the publication of the Diabetes Control and Complications Trial (DCCT) in the 1990s, as individuals treated with CSII in the DCCT had slightly better glycaemic indices than those treated with MDI [27]. This renewed interest in pump therapy coincided with technological advances resulting in improved blood glucose monitoring devices and insulin delivery systems [28]. Since then, CSII has been shown to reduce glycated haemoglobin (HbA_{1c}) as well as the frequency of hypoglycaemia, and it has been incorporated into our management pathways for selected people with type 1 diabetes [29]. However, access to CSII therapy varies greatly depending on location. It is estimated that 11.7% of people with type 1 diabetes in England are using CSII currently, compared to 40% of people with type 1 diabetes in the USA [30].

CSII therapy has significantly progressed since it was first developed (Figure 33.2). Newer models are smaller, more portable and user friendly, and have greater technological capabilities including bolus calculators, advanced bolus delivery options, and the ability to integrate with CGM. *Sensor-augmented pump therapy* refers to CSII systems that integrate with CGM systems, and most systems now feature varying degrees of automation where the system alters insulin delivery in response to sensor glucose readings without input from the user. Artificial pancreas or closed-loop systems represent the most advanced forms of these systems [31].

Features of continuous subcutaneous insulin infusion

Variable basal insulin delivery

The main advantages of CSII are the ability to vary basal rates and the ease of delivery of multiple and more frequent boluses. Basal insulin requirements vary throughout the day, owing to circadian changes in counter-regulatory hormones and insulin sensitivity, behavioural factors (activity, alcohol), and emotional changes (stress) [32–36]. CSII facilitates flexible modulation of basal insulin requirements, depending on demand, to a far greater extent than traditional long-acting insulin taken once (insulin glargine, insulin degludec) or twice daily (insulin detemir). King and Armstrong used CGM data to compare the effect of insulin glargine on nocturnal glycaemia with pre-programmed rates of insulin lispro delivery in individuals using CSII [37]. They reported that those treated with glargine spent more time in hypoglycaemia, and twice the amount of time in the hyperglycaemic range [37]. Their findings were corroborated in a similar study by Bragd et al., who used blinded CGM to compare CSII with basal insulin substitution with insulin glargine in a non-blinded, randomized crossover trial of 15 experienced pump users with type 1 diabetes [38]. They demonstrated improved glycaemic levels with CSII compared to insulin glargine, with a lower mean glucose reading and a greater TIR [38].

There are numerous options for basal rate settings when initiating CSII. The simplest approach is to start with a flat basal rate; that is, 50% of total daily dose (TDD), divided equally over 24 h (Figure 33.3). A flat basal rate will not account for the fluctuating insulin requirements throughout the day, but additional basal rates can then be added according to glucose readings and diurnal variations [40]. Most people with type 1 diabetes will require multiple basal rates throughout the day [41]. Chico et al. assessed insulin requirements in 74 individuals with type 1 diabetes transitioning from MDI to CSII, and found that hourly basal rates were highest late in the evening (dusk phenomenon) and in the early hours of the morning (dawn phenomenon) [41]. Hence, many expert groups recommend the use of a modified circadian basal profile when initiating CSII [42] (Figure 33.3). This usually includes 4–5 basal rate profiles throughout the day, with increased insulin delivery in the early morning and late evening, and reduced insulin delivered in the late night and early afternoon [43].

In children and young adults, studies have reported large variations in basal insulin requirements and circadian insulin profiles between different age groups [39, 44]. As such, some experts have

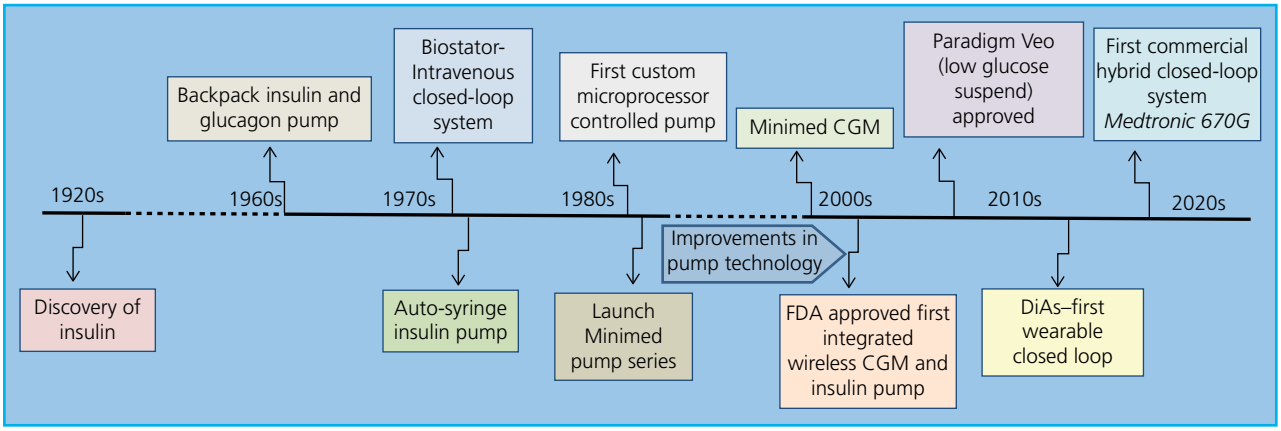

Figure 33.2 Timeline of history of insulin pump technology. CGM, continuous glucose monitoring; DiAs, Diabetes Assistant; FDA, Food and Drug Administration.

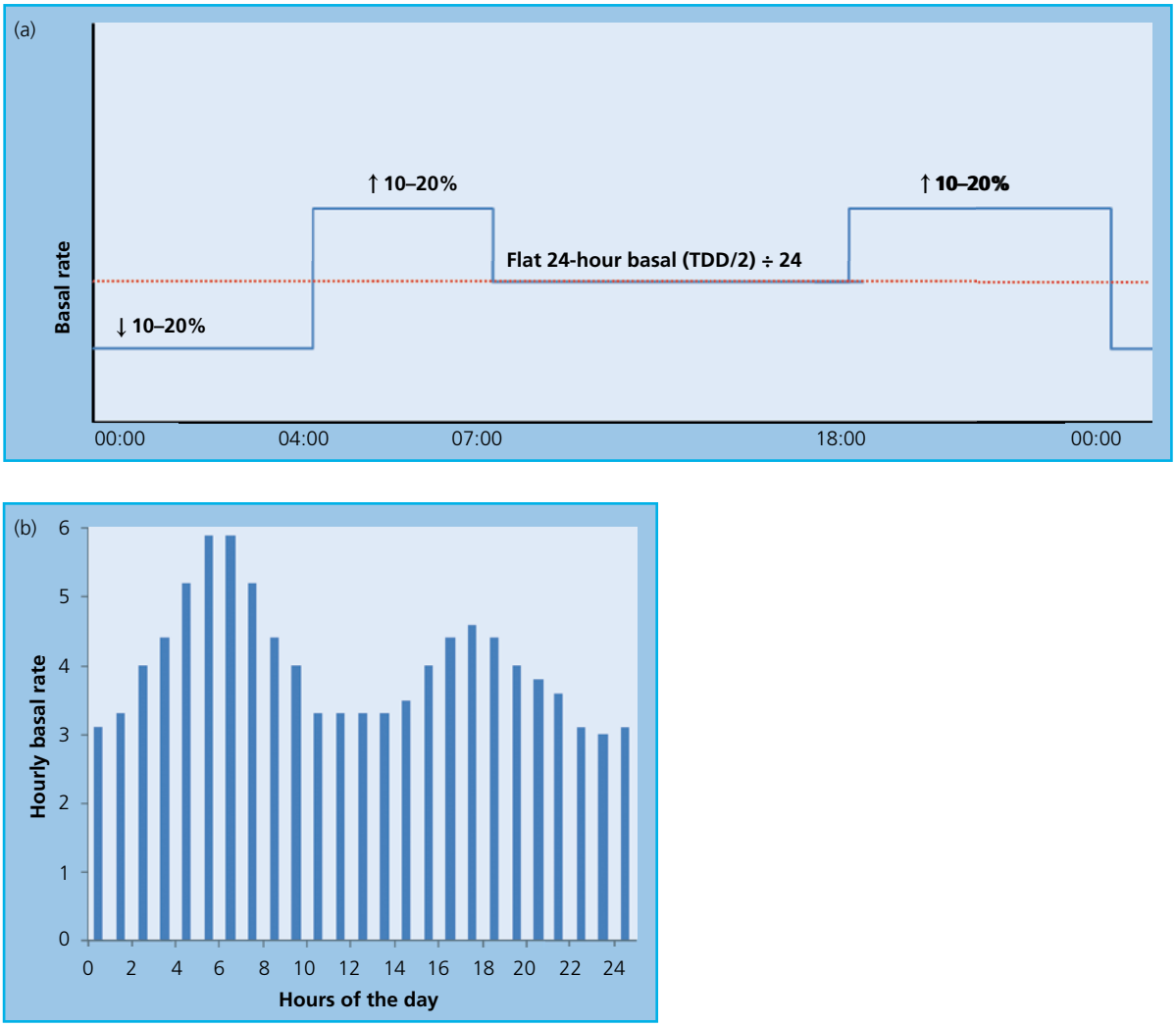

Figure 33.3 (a) Options for basal insulin profile. Broken line represents a flat basal rate over 24 hours. Continuous line represents a modified basal profile. TDD, total daily dose. (b) Options for basal insulin profile based on circadian rhythm, as described by Bachran et al. [39]. The graph depicts requirements for age group 18–24 years.

been advocating a *circadian rhythm*–based basal rate profile when initiating CSII (Figure 33.3b). This involves a double-peaked basal rate profile that mirrors circadian insulin requirements [45]. Much of the research in this area, however, has been conducted in paediatric populations, and there are no clear data of the benefits of a circadian-based profile over a flat basal rate in adults. Although more physiological, there does not appear to be an association between number of basal rates and glycaemic indices such as HbA_{1c} [46]. Laimer et al. also described some concerning associations between high basal rate variability and poor outcomes [45]. In this study of approximately 5000 adults with type 1 diabetes, increased basal rate variability correlated with increased severe hypoglycaemia and diabetic ketoacidosis (DKA) [45]. Recent data from closed-loop studies suggest that overnight basal insulin requirements may vary as much as 200% from day to day, which may explain why it is often difficult to find a basal pattern that offers stability.

Dawn phenomenon

The dawn phenomenon was first described by Schmidt et al. in 1981, when they observed a rise in early-morning fasting blood glucose in 10 of 11 individuals with type 1 diabetes [47]. The dawn phenomenon has been attributed to reduced hepatic and peripheral insulin sensitivity secondary to nocturnal growth hormone spikes [48]. In older studies the magnitude of the dawn phenomenon was greatly exaggerated, as plasma insulin concentrations would fall by dawn, following a nocturnal dose of NPH or lente insulin [49]. The dawn phenomenon is less pronounced with CSII or long-acting insulin analogues, but remains highly variable among individuals [50]. It occurs in approximately 50% of people with type 1 diabetes and is a common indication for CSII therapy [50].

To counteract the dawn phenomenon, insulin pump users often program the pump to deliver increased insulin doses in the early hours of the morning. Though theoretically sensible, the safety and efficacy of this approach were challenged in an eight-month longitudinal study by Bouchonville et al., who used CGM to investigate early-morning CSII programming to manage the dawn phenomenon [51]. In a cohort of 40 people with type 1 diabetes, they reported the occurrence of the dawn phenomenon to a variable extent in all individuals, but a fixed increase in early-morning insulin delivery was found to be ineffective at managing the early-morning hyperglycaemia and increased the risk of hypoglycaemia [51]. In contrast, Lindmeyer et al. recently observed a lower probability of hypoglycaemia (<4.4 mmol/l) and a higher probability of hyperglycaemia (>7.2 mmol/l) in pump users with the most marked dawn

phenomenon, despite increased insulin infusion rates [52]. Although the benefit of CSII for management of the dawn phenomenon may not be as well defined as previously thought, it is likely that it can be mitigated with the judicious use of CGM and an increase in morning insulin delivery.

Temporary basal rates

One of the advanced features of insulin pump therapy is the ability to set short-term temporary basal rates. It is also possible to manually suspend all insulin delivery, including the current basal and any bolus deliveries in progress. The ability to increase or decrease basal insulin delivery by 10–100% is particularly advantageous for managing glucose levels during periods of both increased or decreased activity or during illness. Approximately 60% of pump users utilize this temporary basal function, and there is an association between the habitual use of temporary basal rates and better glycaemic management [53, 54]. People using CSII with CGM are more likely to use temporary basal rates, indicating more active self-adjustment of insulin therapy [55].

Temporary basal rate reduction is most frequently used for managing periods of exercise. In people without diabetes, insulin secretion is significantly reduced during exercise [56]. It is not possible to simulate this physiological reduction in insulin in people with diabetes who have received a basal insulin analogue. However, CSII allows temporary reduction in basal insulin delivery or indeed insulin suspension to compensate for the increased risk of exercise-induced hypoglycaemia. As rapid-acting insulin peaks at 90–100 minutes, it is necessary to adjust the basal rate pre-exercise. A 50–80% reduction in basal insulin delivery 90 minutes before moderate-intensity aerobic exercise reduces the risk of immediate hypoglycaemia [57]. This approach is superior to complete insulin suspension at onset of exercise for both minimizing hypoglycaemia risk without compromising post-exercise glucose levels [57]. CGM studies have demonstrated the risk of delayed hypoglycaemia, which can occur many hours after the activity due to enhanced insulin sensitivity [58]. Hence, a temporary basal rate may be required post activity or during the night after exercise, but this requires individual assessment [59].

Increased temporary basal rates are particularly useful during periods of acute illness or stress or prolonged periods of inactivity (e.g. a long car journey). Increasing basal insulin delivery in these situations can be more effective at managing hyperglycaemia than administering multiple extra correction boluses [58].

A variety of basal rates can be stored in the pump as distinct basal patterns. This feature is particularly useful for people whose daily activities, and thus insulin requirements, vary on a day-to-day basis, such as shift workers. Some women utilize this function to manage their glucose levels during the pre- or peri-menstrual period, though advice in this regard should be individualized.

Bolus advisors

Bolus advisors are provided by most modern pumps and recommend bolus doses of insulin based on target glucose values, insulin sensitivity factor (ISF), predicted carbohydrate intake, insulin-to-carbohydrate ratio (ICR), and current glucose values, while compensating for the IOB from prior boluses. The formula utilized by bolus advisors to recommend an accurate bolus is as follows:

$$\text{Bolus Dose (units)} = [\text{Carbohydrate (g)} \div \text{ICR}] + [(\text{Current glucose} - \text{Target glucose}) \div \text{ISF}] - \text{IOB}$$

Bolus advisors are useful for several reasons. Whatever the mode of insulin delivery, people on intensive insulin therapy must be adept at handling numbers to calculate safe and appropriate insulin doses. National and international surveys have shown that many people lack the basic numerical skills that are essential to maintain their health and make informed medical decisions [60]. Poor numeracy skills are common in people with diabetes and are associated with fewer self-management behaviours and suboptimal glycaemic management [61, 62]. Manual calculation of bolus insulin doses by people with type 1 diabetes is erroneous >60% of the time [63]. Bolus advisors may help overcome the issue of low numeracy in people with type 1 diabetes. Their efficacy was demonstrated by Hommel et al. in a randomized controlled trial (RCT) of people with type 1 diabetes treated with MDI, initiating carbohydrate counting with or without the guidance of an automated bolus calculator [64]. They reported greater reductions in HbA_{1c} in individuals using the bolus calculator compared to those using mental calculations [64]. In other studies, improvements in HbA_{1c} were not seen, but glucose variability was reduced and post-prandial glycaemic excursions were ameliorated [65, 66]. People using bolus advisors also report better treatment satisfaction due to the ease of calculation as well as increased confidence in the accuracy of the dosage and reduced fear of hypoglycaemia [67].

Although user experience with bolus advisors is generally positive, the Relative Effectiveness of Pumps Over MDI and Structured Education (REPOSE) study identified some unintended consequences from offering people this technology [68]. Some people became deskilled and dependent on their advisors as they were no longer calculating their doses [68]. There was also a misconception that pre-programmed bolus advisor parameters did not require review and this, in turn, could negatively impact glycaemic management [68].

One of the benefits of automated bolus advisors is their ability to calculate more precise insulin doses. Precision dosing is an important factor in ensuring the efficacy and safety of insulin treatment, particularly for insulin-sensitive individuals and children and older adults with type 1 diabetes [69]. When used in combination with CSII, insulin doses can be delivered in increments as low as 0.025 units, facilitating greater accuracy in insulin administration, which may lead to improved diabetes management.

After the first bolus of the day, automated bolus advisors account for any residual insulin activity (IOB), so that subsequent boluses are reduced to avoid insulin stacking. This is important, as clamp studies have shown that 40% of insulin aspart (0.2 unit/kg) glucose-lowering activity is still present three hours post subcutaneous injection [70]. Data from paediatric pump users suggest an average daily bolus frequency of 6–7 per day in this cohort [71, 72]. If these boluses are given over an 18-hour waking period, average time intervals between boluses would range from 2.5 to 3 hours. If residual insulin activity is not accounted for, there is a risk of hypoglycaemia due to inevitable insulin stacking.

Bolus advisor users can only reap the benefit of this technology if their parameters are programmed correctly. The correct ICR and ISF should be established prior to setting up the bolus calculator. Residual insulin activity is calculated based on a unique algorithm incorporating the insulin action time (IAT). Currently there is no widely accepted consensus on the IAT for insulin analogues [73]. However, Heinemann and Woodworth demonstrated the variable pharmacodynamics of insulin lispro with different doses, suggesting the need for a shorter IAT (2–3 h) for people with smaller average doses (2–5 units/dose), and a longer IAT (4–5 h) for those with

larger regular doses (>10 units/dose) [74]. The Diabetes Technology Network-UK recommends using an IAT <4 h when the TDD is >30 units/d, and >4 h when the TDD is >60 units/d [42].

Advanced bolus options

Most modern pumps offer a range of bolus options (Figure 33.4). The advanced bolus option offers the chance to tailor the delivery of the bolus dose, according to the composition of the meal and the expected effects on glycaemia; however, this is not widely used in clinical practice. An extended or square-wave bolus of insulin is delivered over a set period of time as opposed to an upfront standard bolus of insulin. It can be given over several minutes up to a number of hours and can be useful to manage high-fat and high-protein meals. The dual-wave or multiwave bolus involves an instant bolus followed by an extended bolus, and it is effective at controlling postprandial glucose levels after high-carbohydrate, high-fat meals [75]. Indeed, use of dual-wave boluses has been associated with better glycaemic levels in some small studies [76,77]. However, these results are somewhat compounded by the fact that people using advanced bolus options may have an improved understanding of diabetes and more confidence in self-management of their insulin therapy.

Sensor-augmented pump therapy

The augmentation of pump therapy with integrated real-time CGM creates the opportunity to automate insulin delivery based on sensor values and has been shown to improve glucose levels and reduce hypoglycaemia [78,79]. Threshold-suspend systems suspend basal insulin delivery once a low glucose value is reached, while predictive-suspend systems suspend basal insulin delivery in response to predicted hypoglycaemia. These systems have been shown in large-scale RCTs to reduce the duration of and frequency of hypoglycaemia, respectively [80,81]. In particular, the predictive low glucose suspend feature demonstrated an 87% reduction in rates of severe hypoglycaemia in a high-risk population with impaired awareness and was associated with a high degree of satisfaction and a feeling of increased security, particularly at night [82,83].

Hybrid closed-loop technology is currently the most advanced form of insulin delivery available. It utilizes a control algorithm, which automatically adjusts basal insulin delivery every few minutes based on sensor glucose levels, but requires the user to calculate and deliver meal-related boluses. These hybrid closed-loop systems significantly improve glycaemic indices with real-world experience demonstrating TIR >70% [84]. As hybrid closed-loop systems do not fully automate diabetes management, users must be educated and motivated to derive the maximum benefit from the system [85], with some studies showing that up to 30% of users stop using them over time. More advanced systems, with reduced need for sensor calibrations, more aggressive algorithms, and simpler or absent requirements for food-related boluses are in development.

Do-it-yourself artificial pancreas system

The term do-it-yourself artificial pancreas system (DIY-APS) describes the automated closed-loop insulin delivery system developed by members of the diabetes community that uses CGM, an algorithm to calculate insulin doses, a communication device, and an insulin pump [86]. As the algorithm is unauthorized, these devices are not approved, commercialized, or regulated [11]. Driven predominantly by the #WeAreNotWaiting community, there has been rapid growth in the use of DIY closed-loop systems worldwide over the last number of years [87]. There are currently three forms of DIY-APS in use: OpenAPS, AndroidAPS, and Loop [86]. In general, DIY-APS work similarly to commercially available closed-loop systems, but DIY systems may offer users improved interoperability and customizable settings [88]. In contrast to commercially available closed-loop systems, advances have been made in DIY algorithms such that the second-generation DIY-APS are fully automated and meal/carbohydrate announcements are not required [89].

Real-world evidence for DIY-APS has been overwhelmingly positive, though these studies are limited not only by the small self-selecting population of tech-savvy people with diabetes who are highly engaged in the management of their diabetes, but also by the subjectively reported outcomes. Melmer et al. analysed data from 80 OpenAPS users and found that mean TIR achieved by this cohort was 77.5%, with just 4.3% time below 3.9 mmol/l [90]. Quality-of-life outcomes have also been reported by DIY system users. In a qualitative analysis of more than 3000 tweets from 328 people with type 1 diabetes or caregivers, the overarching sentiment emerging from the data was that OpenAPS reduced diabetes-related burden and distress [91]. The main disadvantages of DIY-APS relate to the technical and hardware limitations of old or out-of-warranty pumps or potential problems that may arise with an unregulated, unapproved algorithm [86]. Furthermore, healthcare professionals often feel uncomfortable supporting people with diabetes who use these systems because of a lack of knowledge of the system or because of fears of indemnity. However, in a recent survey of UK practitioners, 97% of respondents reported that healthcare professionals should learn more about DIY-APS to improve their ability to support users of these systems [92].

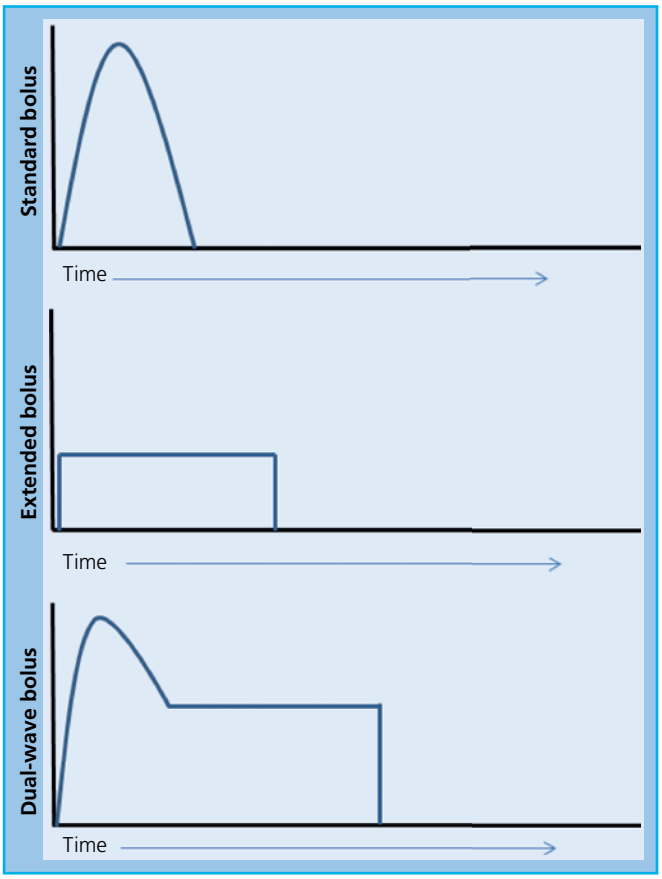

Figure 33.4 Standard, extended, and dual-wave bolus insulin delivery options.

Evidence base for pumps

The evidence base for pumps is derived from both RCTs and real-world evidence. RCTs of pumps are often limited by short study duration, a carefully selected population, and the fact that they are conducted under specific, tightly controlled conditions. Furthermore, as early studies of CSII versus MDI were conducted using older basal insulins, many RCTs are not typically representative of routine current clinical practice. Real-world evidence has advantages over RCTs, including lower costs, fewer restrictions in population inclusion, and longer timeframes [93]. In this context, large population-based cohort studies complement the evidence generated from RCTs. The following sections will explore the available evidence for CSII under a number of subheadings.

Glycaemic management

Numerous older studies demonstrated the superiority of CSII over MDI in improving glycaemic levels and reducing glucose variability, but these benefits were less pronounced in studies using more modern basal insulin analogues. In a meta-analysis published in 2008, Pickup et al. evaluated three RCTs and one before/after study that compared glycaemic levels achieved using insulin glargine–based MDI with CSII [94]. Although the studies were of short duration (1.25–6 months), the mean HbA_{1c} difference between glargine-based MDI and CSII was 0.63% (7 mmol/mol) in favour of CSII [94]. In a more recent meta-analysis conducted by Pala et al., the evidence comparing CSII with modern MDI regimens was again reviewed [95]. In trials where rapid-acting analogues were used, the advantage of CSII was significantly smaller than in trials with regular human insulin and CSII (−0.29% vs −1.93%; −3 mmol/mol vs 21 mmol/mol) [95]. A similar modest reduction in HbA_{1c} (−0.37%, 4 mmol/mol) was demonstrated by Benkhadra et al. in their analysis of 25 RCTs comparing CSII with MDI in both adults and children with type 1 diabetes [96], echoing the previous findings of a Cochrane review in 2010 [97].

There is little information on the comparative effectiveness of CSII and MDI over longer periods. Real-world evidence suggests minor sustained improvements in HbA_{1c} with pump therapy. In a Swedish observational study of almost 300 individuals with type 1 diabetes using CSII therapy, Carlsson et al. demonstrated that the improvements in HbA_{1c} persisted at five-year follow-up, but the effect of CSII on glycaemic management diminished over time [98]. Similar findings were reported by an Australian group that had up to eight years of follow-up data for some of its pump users [99]. In this study, greater HbA_{1c} reductions occurred in those with higher HbA_{1c} levels at CSII commencement, a common theme in pump studies, and the greatest reduction in HbA_{1c} occurred at one year [99]. Beato-Vibora et al. reported greater benefits in HbA_{1c}, with a mean reduction of 1.1% (12 mmol/mol) sustained over five years, in more than 300 pump users in a single-centre UK study [100]. Overall, it seems that there are variations in long-term efficacy of CSII. In another UK study, Nixon et al. categorized 35 adults with type 1 diabetes into subgroups according to their response to pump therapy [101]. They reported that 57% of people had an initial improvement in HbA_{1c} followed by a deterioration, 31% had sustained glycaemic improvement over four years, and 12% were non-responders [101].

When comparing CSII with MDI, it is very difficult to control for the confounding effect of the intensive diabetes self-management education and increased healthcare access associated with the commencement of CSII therapy. The REPOSE study tried to address this issue and is the longest and largest RCT of CSII in type 1 diabetes [102]. In this study, the efficacy and cost-effectiveness of CSII therapy were compared to an MDI regimen in 317 adults with type 1 diabetes, when both groups received equivalent structured training in flexible insulin therapy [102]. It is noteworthy that the participants in this study had no preference for either MDI or pump therapy, and individuals with a strong desire for pump therapy were excluded. In addition, the individuals had no clinical indication for pump therapy. The trial participants had longstanding diabetes (approx. 18 years) and suboptimal glycaemic levels at baseline (mean HbA_{1c} 9.1%; 76 mmol/mol) [102]. The individuals were followed for two years and the primary outcomes were change in HbA_{1c} from baseline and the proportion of individuals achieving HbA_{1c} <7.5% (58 mmol/mol) [102]. Both groups achieved clinically significant improvements in both glycaemic levels and rates of severe hypoglycaemia [102]. Although the improvement was slightly greater in the pump group, this did not reach statistical significance in the primary analysis [102]. The treatment difference was significantly greater in the per protocol analysis in favour of CSII ($p = 0.02$) [102]. The number of episodes of DKA was greater in the CSII group compared to those on MDI [102]. In this study, CSII was only superior to MDI in relation to treatment satisfaction and some quality-of-life domains [102]. This benefit of CSII therapy on quality of life has been shown previously and will be discussed later in this chapter.

The effect of CSII therapy on glycaemic measures has also been studied in other populations, with varying success. In a recent RCT conducted in the UK, the efficacy, safety, and cost utility of CSII were compared with MDI in children between 7 and 15 years, during the first year following diagnosis of type 1 diabetes [103]. Again, all participants in this trial completed a structured education programme and there was no clinical benefit of CSII over MDI in this cohort [103]. Furthermore, neither regimen was successful in achieving optimum glycaemic targets [103]. Interestingly, observational studies investigating CSII use in paediatric populations with longer duration of diabetes have reported better outcomes. Korkmaz et al. compared long term glycaemic outcomes in 52 individuals with type 1 diabetes treated with CSII to 38 age- and sex-matched MDI-treated controls [104]. The mean duration of diabetes in the study cohort was 10.7 years, and in this study CSII was associated with better glycaemic levels in all ages and at all times over a five-year period, compared to MDI [104]. In another retrospective multicentre study of pump use in children and adolescents with type 1 diabetes for an average of 6.3 years, CSII was associated with significant improvement in HbA_{1c} during follow-up, but the major benefit was in boys only [105].

A higher number of capillary blood glucose measurements and a higher daily number of boluses are associated with better glycaemic levels in children and adults [106, 107]. Hence, it is unsurprising that the use of real-time CGM, in addition to pump therapy, results in improved HbA_{1c}, as demonstrated in the Sensor-augmented pump Therapy for A1C Reduction (STAR-3) study. In this large one-year, multicentre RCT comparing sensor-augmented pumps to MDI in almost 500 people with type 1 diabetes, mean HbA_{1c} dropped by 0.8% (9 mmol/mol) in the sensor-augmented pump group compared to 0.2% (2 mmol/mol) in the MDI group [108]. It is noteworthy that participants in the sensor-augmented pump group had more clinical contacts than the MDI group in the first five weeks of the study [108]. The additional training and education received by this group may well have contributed to the favourable outcomes. The real-world Comparison of Sensor-Augmented Insulin Regimens (COMISAIR) study suggests that the benefit of sensor-augmented pumps is derived mostly from real-time CGM.

In their non-randomized, prospective clinical trial, Šoupal et al. found that after three years' follow-up, CGM with MDI performed as well as CGM with CSII at improving glycaemic levels, increasing TIR and reducing hypoglycaemia [109].

CSII may be advantageous in pre-pregnancy and pregnancy. Women with pre-gestational type 1 diabetes have an increased risk of adverse outcomes, including spontaneous abortions, congenital malformation, macrosomia, pre-eclampsia, need for operative delivery, and progression of diabetes complications [90]. In a study of women with type 1 diabetes attending a clinic for pre-pregnancy care, individuals using CSII had lower HbA_{1c} levels at booking compared to those on MDI [110]. In another observational study of 128 pregnant women with pre-gestational type 1 diabetes, CSII compared favourably with MDI in reducing HbA_{1c} and glycaemic variability during the pre-conception period and during each trimester of pregnancy [111]. Rys et al. published a systematic review and meta-analysis of 47 studies, including 43 non-RCTs, with data on almost 8000 pregnancies in women with type 1 diabetes, evaluating CSII versus MDI in pregnancy [112]. HbA_{1c} was lower in pump users compared to MDI in the first trimester, but the difference in HbA_{1c} between the two groups decreased in subsequent trimesters [112]. They postulated that the better glycaemic management observed in the CSII group in the first trimester could be attributed to greater participation in pre-conception care by this cohort [112]. The difference in glycaemic levels between the two groups diminished as the pregnancy progressed, suggesting that good glycaemic management is possible with either method of insulin delivery when the woman is highly motivated to self-manage her diabetes. In terms of materno-fetal outcomes, this review demonstrated increased maternal gestational weight gain and increased large for gestational age babies in the CSII group [112]. This observation was also reported by Hauffe et al., and emphasizes the importance of education on gestational weight gain for women with type 1 diabetes who are planning pregnancy [113].

The use of CSII for the treatment of type 1 diabetes in older adults is becoming increasingly popular. A recent report from the Diabetes Prospective Follow-up Registry compared diabetes-related outcomes in older adults with type 1 diabetes using CSII versus MDI [114]. CSII was associated with slightly better glycaemic levels and lower rates of severe hypoglycaemia and DKA, suggesting that older age itself should not be considered a contraindication to insulin pump therapy [114]. Although not routinely used in clinical practice, there is also evidence that people with type 2 diabetes may benefit from CSII. The OpT2mise Glucose Control in Type 2 Diabetes Mellitus with Insulin Pump Therapy study was a multicentre randomized open-label trial of CSII versus MDI in individuals with suboptimally managed type 2 diabetes [115]. At six months, there was a significantly greater reduction in HbA_{1c} in the CSII group compared to the MDI group [115]. A meta-analysis of five RCTs comparing CSII to MDI in the treatment of type 2 diabetes concluded that CSII is superior to MDI in individuals with suboptimally managed type 2 diabetes and is associated with a reduction in insulin requirements and no weight gain [116]. The individuals with the highest HbA_{1c} at baseline and the highest insulin requirements seemed to benefit most from CSII [116].

Healthcare professionals find it difficult to predict who gains the most benefit from insulin pump therapy. Though multiple guidelines recommend the use of CSII for those with problematic hypoglycaemia, pump therapy can confer additional benefits outside of this setting, particularly in the form of improved glycaemic management [117]. Unfortunately, clinicians are inherently biased when it comes to determining suitability for CSII, as many are concerned that the technology may be too complex or advanced for some individuals [118]. Staff involved in the REPOSE study reported being surprised by how well some individuals, for whom CSII would not have been recommended in routine clinical practice, managed their insulin pump regimen [118]. This further supports the need for healthcare professionals to challenge their personal beliefs and views regarding suitability for this therapy.

Hypoglycaemia

The greatest risk of intensive insulin treatment is hypoglycaemia. Tight glycaemic management in the intensive arm of the DCCT was associated with a threefold increased risk of severe hypoglycaemia [27]. CSII is often recommended for people with type 1 diabetes whose attempts to achieve target HbA_{1c} on MDI are hampered by disabling hypoglycaemia despite dose optimization and adequate healthcare provider support. Although this cohort of people with type 1 diabetes are difficult to study, as people with impaired awareness of hypoglycaemia or a history of severe hypoglycaemia are often excluded from clinical trials, there is both RCT and real-world evidence to support the use of CSII in this cohort.

In a large study of 75 adolescents and young adults, aged 12–20 years, receiving intensive insulin treatment, CSII reduced the rate of severe hypoglycaemic events by 50% compared to MDI without adversely affecting glycaemic levels [119]. Although this was a prospective study, it is limited by its non-randomized nature. The participants in this study who received CSII therapy chose CSII as their preferred mode of treatment, which may reflect higher levels of motivation or a greater understanding of diabetes self-management compared to the MDI group [119]. Similar large reductions in severe hypoglycaemia rates were reported in the 2008 meta-analysis by Pickup and Sutton [94]. This meta-analysis of studies comparing the frequency of severe hypoglycaemia during CSII and MDI therapy only included studies published during or after 1996, where duration of CSII treatment was >6 months, and rate of severe hypoglycaemia on MDI was >10 episodes per 100 person-years [94]. Although this showed that severe hypoglycaemia was reduced with CSII compared to MDI (rate ratio 4.19 for all studies), all MDI regimens in these studies were based on isophane- or lente-type intermediate-acting insulin in combination with regular or monomeric mealtime insulin. Hence, these results cannot be extrapolated to a population using newer long-acting insulin analogues, as is the current practice. Interestingly, in a small randomized pilot study of 21 individuals with type 1 diabetes complicated by severe hypoglycaemia, optimizing analogue therapy had similar efficacy to CSII in restoring hypoglycaemia awareness and preventing further episodes of severe hypoglycaemia [120].

The Hypo-compass trial was a 2×2 factorial RCT comparing CSII and MDI with or without CGM in 96 individuals with type 1 diabetes and impaired awareness of hypoglycaemia [121]. The aim of the intervention was rigorous avoidance of biochemical hypoglycaemia without relaxing overall glycaemic management [121]. All individuals received comparable education in the form of a 1–2-hour hypoglycaemia psycho-education session, and intense clinical support for the six-month trial. At 24 weeks, there were similar reductions in severe hypoglycaemia (over 10-fold) and improvements in hypoglycaemia awareness between groups, though treatment satisfaction was higher in the CSII group [121]. Although the individuals returned to routine care after 24 weeks, these improvements were sustained at 24-month follow-up [122]. It was

surprising that this study did not show any differences in outcomes between CSII and MDI groups, but it is notable that the MDI group in the Hypo-compass trial were managed with a twice-daily basal analogue regimen, utilized a bolus calculator, and received weekly phone calls and monthly visits for the first six months. This was not the case in the studies included in the meta-analysis by Pickup and Sutton [94]. Significant improvement in the control arms due to these factors may partly explain the apparent lack of benefit from CGM or CSII in this study.

Real-world evidence demonstrates that CSII reduces the burden of hypoglycaemia. In a large retrospective analysis of more than 300 adult CSII users, the percentage of individuals with >5 mild or moderate hypoglycaemic events per week reduced from 29% to 12% [100]. In addition, the frequency of severe hypoglycaemic episodes halved from 0.6 to 0.3 per year [100]. This reduction in hypoglycaemia was sustained over a mean follow-up of 4.3 years [100]. These findings have been corroborated in other retrospective observational studies evaluating the efficacy of CSII in children, adolescents, and adults with type 1 diabetes, and reductions in both mild, moderate, and severe hypoglycaemia have been reported [123–125]. In general, people with a high burden of hypoglycaemia at baseline tend to derive the most benefit from CSII therapy [126].

Late complications

Few studies have examined the effect of CSII on long-term complications in people with type 1 diabetes. Zabeen et al. compared rates of microvascular complications in adolescents and young adults with type 1 diabetes treated with either CSII or MDI for at least 12 months [127]. In this cohort of almost 1000 individuals, glycaemic levels were equivalent between groups, but CSII use was associated with lower rates of retinopathy and peripheral nerve abnormalities compared to MDI [127]. The potential beneficial effect of CSII on glycaemic variability may be responsible for the findings [127]. Similarly, Downie et al. demonstrated in a subgroup analysis of their study that, despite similar HbA_{1c} levels, there was reduced risk of retinopathy in people with type 1 diabetes who were treated with CSII compared to MDI [128]. In another study assessing the effect of CSII on the development of microalbuminuric nephropathy, Lepore et al. compared the albumin excretion rate in 110 individuals using CSII to 110 people using MDI. Although albumin excretion rate at baseline was similar in both groups, albumin excretion rate was significantly lower in the CSII group at two- and three-year follow-up [129]. The results of this study are confounded, however, by the improved glycaemic levels in the CSII group compared to the MDI group at follow-up (HbA_{1c} 8.1% vs 8.4%; 65 mmol/mol vs 68 mmol/mol) [129].

In 2015, Steineck et al. published a large nationwide observational study investigating the relationship between insulin pump treatment and cardiovascular mortality [130]. Data were obtained from the Swedish national diabetes register on more than 18 000 people with type 1 diabetes, of whom almost 2500 were using insulin pumps [130]. After a mean follow-up of 6.8 years, CSII was associated with significantly reduced fatal coronary heart disease (45%), fatal cardiovascular disease (42%), and all-cause mortality (27%) [130]. It is unclear if the improved cardiovascular outcomes seen in the CSII group were related to direct treatment effect, or if they were attributable to potential increased education, monitoring, and self-management skills in this group. It is also plausible that reduced hypoglycaemia and less glucose variability in pump users contributed to the beneficial effects on cardiovascular disease. Further prospective studies, with long-term microvascular and macrovascular outcome data, are required before we can infer a true cause–effect relationship between CSII and diabetes-related complications.

Quality of life

Many RCTs comparing the efficacy of CSII with MDI also reported quality-of-life outcomes. As mentioned, pump users in the REPOSE trial reported greater improvement in treatment satisfaction and in some quality-of-life domains (dietary freedom and daily hassle of functions) compared to the MDI group [102]. The Pumps for Kids, Infants, and Neonates (PumpKIN) trial was a multicentre RCT of children (aged 6–16 years) with type 1 diabetes randomized to commence CSII or remain on MDI for six months [131]. In this study, CSII therapy was associated with significant improvements in diabetes health-related quality of life in younger children, and the caregivers of the CSII group also reported a significant decline in overall diabetes burden compared to the MDI group [131].

Most of the evidence for quality-of-life benefits with pump therapy comes from real-world evidence. In a study comparing health-related quality of life in more than 200 youths with type 1 diabetes treated with either CSII or MDI, pump users reported significantly better quality of life compared to those on an MDI regimen [132]. Although there were no differences in glycaemic levels or physical fitness between the two groups, CSII use was associated with better physical, emotional, and school-related functioning and reduced diabetes-related worry [132]. Other studies have reported consistent findings when parents were used for proxy reporting on their child's quality of life [133, 134]. An Italian study of more than 500 adolescents between 10 and 17 years of age also indicated that CSII was associated with better health-related quality of life than MDI [135]. CSII users reported improved treatment satisfaction and perceived clinical efficacy, and reduced interference with daily activities [135]. Interestingly, in this study, CSII performed better in those with lower quality-of-life scores, suggesting that those with perceived low quality of life may gain benefit from pump therapy [135].

Adults have also reported improved quality of life on CSII. In a small qualitative study of Kuwaiti adults with type 1 diabetes recruited from pump clinics, CSII had positive impacts on the quality of life of participants, primarily by enhancing lifestyle flexibility [136]. Quirós et al. found the user experience of adults CSII users to be very positive, with 93% of participants reporting that they would not return to their previous insulin treatment [137]. These results are discordant with those reported by Reddy et al., who investigated the effect of glycaemic variability on quality of life in adults with type 1 diabetes [138]. Almost two-thirds of participants were on CSII and although glycaemic variability was lower in this group, there were no significant differences in diabetes-related quality of life between CSII and MDI groups [138]. Although this study and few others suggest that quality of life in CSII users is equivalent or even inferior to those on MDI, comparison between studies is difficult as inconsistent assessment and poor trial methodology often cloud the issue [139].

Cost-effectiveness

With the rapid evolution of technologies for treatment of type 1 diabetes, economic evaluations are required to guide policy making. Although CSII has benefits in terms of glycaemic management, hypoglycaemia, complications, and quality of life, these must be weighed against the cost of standard care with MDI. A recent systematic review of 35 studies investigating the cost-effectiveness

of diabetes technologies concluded that insulin pumps were cost-effective, particularly for those with suboptimal glycaemic management or high levels of hypoglycaemia [140]. In this meta-analysis, CSII in conjunction with self-monitoring blood glucose was cost-effective compared to MDI with self-monitoring blood glucose in 56% of studies reviewed [140]. Incremental cost-effective ratios (ICERs) below willingness-to-pay thresholds ranged from $21 000 to $57 000 per quality-adjusted life year (QALY) gained in the USA [141, 142]. In contrast, a health economics analysis of the REPOSE study, which compared pumps with MDI with equivalent structured education in both groups, indicated that the ICER was unlikely to fall below a threshold of £30 000 per QALY gained, and therefore was not considered cost-effective in those without an immediate clinical need [30].

Determinants of cost-effectiveness of diabetes therapies are largely based on changes in HbA_{1c} and rates of hypoglycaemia. HbA_{1c} is used to predict long-term complications and hypoglycaemia contributes to costs incurred from lost productivity, ambulance call-outs, emergency department attendances, and so on [140]. Therefore, cost-utility analyses of CSII compared to MDI are influenced by the predetermined modelled treatment effects in favour of a specific therapy. Older studies conducting economic evaluations on CSII versus MDI modelled HbA_{1c} reductions of 0.6–1.2% (7–13 mmol/mol) in favour of pump therapy based on meta-analyses by Weissberg-Benchell et al. and Pickup et al. [28, 143]. This may have led to the long-term benefits of CSII therapy being overestimated, considering that recent data suggest more modest reductions in HbA_{1c} [95, 96, 144]. However, any positive bias towards CSII may be offset by the conservative assumption that hypoglycaemia rates were equivalent in both CSII and MDI groups in many studies. When the treatment effect for hypoglycaemia prevention is increased, ICER is reduced significantly [140]. Many trials are not adequately powered to draw definitive conclusions about treatment effects on severe hypoglycaemia, and the short duration of RCTs suggests that they may not be suitable for long-term modelling of hypoglycaemia risk [140]. In summary, although ICERs vary widely, the current economic literature suggests cost-effectiveness of CSII, especially in populations with the most to gain.

Types of pumps

Conventional pumps comprise a small digital device that continuously delivers rapid-acting insulin through a catheter inserted into the subcutaneous tissue, which is fixed in place with an adhesive. Most infusion catheters are connected to the pump by plastic tubing. In contrast, tubeless pumps (also called patch pumps) do not use plastic tubing and adhere directly to the skin. Insulin is delivered through the infusion catheter. Insulin delivery is controlled by a remote device through wireless technology [145]. Patch pumps can deliver basal insulin, bolus insulin, or both and are used by about 5% of people utilizing insulin pumps [146].

There are both simplified and advanced patch pumps available, with the more simplified versions geared towards type 2 diabetes management. These are primarily used as pen replacements, are fully disposable, and are changed daily [146]. The advanced patch pumps are flexible devices, which have all the features to manage a complex insulin regimen [146]. There are some advantages of patch pumps over conventional tubed pumps. Firstly, upfront costs are lower, and as patch pumps are disposable, a four-year commitment to CSII therapy is not necessarily required and new pump users can be transitioned back to MDI if they are struggling on their new regimen. Secondly, patch pumps are smaller and more discreet than conventional pumps, and since they attach directly to the skin, there are no issues with insulin infusion sets. Insulin infusion sets are problematic as they require priming and are prone to clogging, kinking of tubing, and obstruction of insulin delivery by air bubbles [147]. In a survey of people with type 1 diabetes using conventional pumps, kinking and blockage were the commonest infusion set problems and were reported in more than 50% of respondents [148]. Another advantage of the patch pump is that it can be attached to many different parts of the body, which is useful for individuals with abdominal lipohypertrophy. Finally, many are water resistant and can be used while showering or swimming [147]. There are also some limitations of the patch pump. If the device is removed for any reason, it must be disposed of and a fresh patch pump reinserted. This can lead to increased waste in plastic, materials, and batteries. The requirement for an additional device to control the infusion of insulin is also a disadvantage of patch pumps. If the pump user misplaced or forgot to carry the device, bolus insulin delivery would not be possible in its absence.

Currently, there is a paucity of RCT data and limited real-world evidence comparing tubed and tubeless pumps. Leelarathna et al. conducted a retrospective observational study comparing glycaemic outcomes with different types of insulin pumps in a large cohort of more than 500 adults with type 1 diabetes [149]. They observed no difference in HbA_{1c} lowering between patch pumps and conventional tubed pumps [149]. Data on quality of life were not collected, which is a limitation of this study, as patch pump users are widely satisfied with this treatment [150]. Although patch pumps are an exciting new tool in the diabetes armour, there is a need for more robust evidence to guide their use prior to widespread adoption into clinical practice.

Types of cannulas

Insulin pumps are manufactured with either steel or Teflon (polytetrafluoroethylene) cannulas. Teflon catheters are preferentially used in the USA and in Europe, with the exception of Germany, where approximately 40% of the cannulas are steel [151]. There are advantages and disadvantages to both. Steel catheters are easier to insert and are less prone to kinking and dislodgement [151]. They may cause more discomfort, however, particularly during exercise, and may be associated with more bleeding [152]. Auto-insertion devices are not used with steel cannulas, which may be problematic for individuals with needle phobias or issues with dexterity. Furthermore, steels sets need to be changed every two days, whereas Teflon sets require changing every three days [151].

There is a dearth of evidence comparing insulin infusion sets. Patel et al. conducted a randomized open-label crossover study, comparing steel to Teflon catheters in insulin pump therapy in people with type 1 diabetes. In this extended-wear study, where infusion sets were worn until failure or up to one week, there was no difference in their function over seven days, but there was a 15% initial failure rate with the Teflon sets due to kinking [153]. At seven days, both types of infusion sets had a 64% failure rate, with the commonest causes of failure being hyperglycaemia and pain [153]. In an *in vivo* study of the inflammatory tissue response to steel and Teflon cannulas in swine, there was no superiority of one material over another in terms of inflammation [152]. This is important, as Eisler et al. previously demonstrated that tissue inflammatory response directly affects bolus shape and tubing pressure in large swine receiving continuous insulin delivery via Teflon infusion sets [154].

Although Teflon cannulas appear to be more popular than steel at the moment, the evidence is equivocal in favour of or against either material. As steel cannulas are cheaper and associated with fewer set failures, people should be offered a choice of cannula, unless there is a clear predisposing reason to opt for one over the other [151].

Insulin pump–associated adverse events

The most common insulin pump–associated adverse events include pump malfunction, infusion set blockage, site issues, and cutaneous problems. These adverse events predispose the person with diabetes to developing hyperglycaemia and ketosis [155]. Adverse events occur in 40% of pump users per year and a small proportion require hospital admission as a result [155]. There are no clear predictors of pump-associated adverse events, although longer duration of pumping may be protective [156]. There does not appear to be any relationship between pump-associated adverse events and glycaemic levels, socioeconomic status, pump manufacturer, or infusion set type [156, 157].

Pump malfunction or pump failure is common. In a prospective observational study, Guenego et al. analysed all insulin pump defects in a cohort of 350 pump users and found that malfunctions occurred in 68% of pumps [158]. The majority of these (44%) were minor defects, 35% were mechanical defects, but 12% represented complete failures, although hyperglycaemia only occurred in 2.9% of cases [158]. These rates of pump failure are consistent with other studies. In a large Italian cohort of more than 11 000 children and adolescent pump users, 11.8% of pump replacements were due to pump failure [159]. In cases of pump failure or malfunction, the device is often returned to the manufacturer for analysis and replaced with a new pump.

Insulin infusion sets are sometimes referred to as the Achilles' heel of CSII therapy. There are numerous types of insulin infusion sets, which vary depending on the angle of insertion into the skin, the length of the cannula, the tubing material, and the length of the tubing [147]. Technical issues arising from insulin infusion sets may be related to kinking or bending of the cannula, displacement of the attachment on the skin, or occlusion of or leakage from the infusion set. All of these can result in DKA. Using an auto-inserter, ensuring the adhesive is attached correctly, and using additional tape if required can minimize these complications [147]. The presence of subcutaneous lipohypertrophy and the use of insulin infusion sets for longer than the recommended period of time predispose to the development of infusion set–related adverse events [160, 161].

The absence of long-acting basal insulin in pump users contributes to the rapid development of DKA in the event of insulin infusion set failures. The theoretical increased risk of DKA means that CSII therapy was often considered a dangerous treatment regimen for people with type 1 diabetes. However, recent data suggest that DKA rates in pump users are no higher than in those on MDI [162, 163]. In fact, in clinics managing large numbers of people on CSII (>250 individuals), DKA rates were actually lower among CSII users [163]. This is likely due to improved diabetes self-management education. Practical guidance to avoid ketosis is given at initiation of pump therapy, and most individuals are advised to change infusion sets in the case of two consecutive high glucose readings that have not responded to a correction bolus.

Skin reactions in response to CSII are often reported in both paediatric and adult populations with type 1 diabetes. In one study of 111 adults, 64% reported skin problems related to pump therapy, with itching being the most common complaint. This also led to increased disease burden and emotional distress [164]. High rates of skin irritation by the adhesive tapes contained in the insulin infusion sets have consistently been reported in many other studies [165, 166]. Erythema, pruritus, pain, scars, or lipohypertrophy are some of the other cutaneous complications that have been reported by users of CSII therapy [147]. Inadequate disinfection of the insertion site or infrequent changing of insulin infusion set may predispose to dermatological complications [147].

Intraperitoneal pumps

Continuous intraperitoneal insulin infusion (CIPII) refers to continuous insulin delivery directly into the peritoneal cavity [167]. This mode of insulin delivery more closely mimics physiological insulin secretion, as insulin rapidly enters the portal venous system and therefore the onset of insulin action is faster than with subcutaneous insulin [168]. Intraperitoneal pumps are a valuable option for people with diabetes in whom subcutaneous insulin therapy fails, and can be offered to those with severe subcutaneous insulin resistance, suboptimal glycaemic levels, marked glucose fluctuations, or recurrent severe hypoglycaemia, despite intensive education and follow-up on a subcutaneous insulin regimen [169].

For CIPII, a catheter is placed within the peritoneal cavity and attached to either an insulin pump implanted in the abdominal wall or a percutaneous port that is connected to an external insulin pump. To date, most clinical experience of CIPII has been with implantable pumps and evidence suggests that implantable intraperitoneal pumps significantly reduce glycaemic fluctuations and improve quality of life in people with both type 1 diabetes and type 2 diabetes [169]. Percutaneous port systems such as the Accu-Chek® DiaPort (Roche Diabetes Care, Indianapolis, IN, USA; Figure 33.5) improve quality of life and reduce hypoglycaemia compared to CSII [170]. Infections, insulin underdelivery, and abdominal pain are the most commonly reported complications of CIPII [169, 170]. The increased complication rates, the invasiveness of CIPII, as well as the need to permanently wear an implanted device will likely continue to limit the widespread use of CIPII in the future, particularly as insulin pump and CGM technology continues to improve.

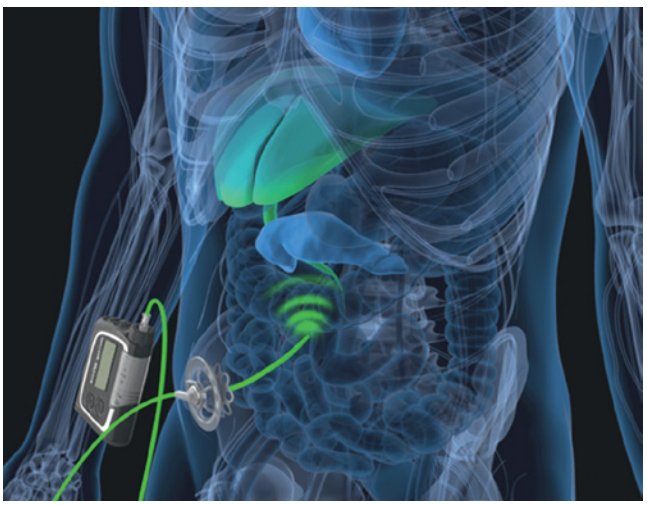

Figure 33.5 Accu-Chek® DiaPort system. Source: With permission from Roche.

Future prospects

Although huge progress has been made in improving delivery systems for insulin administration over the last 20 years, the future looks bright, with exciting new technologies on the horizon. Glucose-responsive smart insulin systems aim to provide insulin action commensurate to the glycaemic state of the person [171]. Algorithm-based glucose-responsive insulin systems already exist in the form of closed-loop systems with CGM and CSII. Another glucose-responsive insulin is the polymer-based system, in which insulin is encapsulated within a glucose-responsive matrix suitable for subcutaneous injection, which senses ambient glucose concentrations and releases a proportional amount of insulin for systemic absorption [171]. Thus, these matrices are impermeable to insulin in normo- or hypoglycaemic conditions, and the permeability of the polymer increases in response to a rise in interstitial glucose concentrations [171]. Insulin or its formulation can also be manipulated at a molecular level, to confer glucose-dependent activity, and this is another avenue for glucose-responsive insulin design [171, 172].

Transdermal insulin delivery via microneedles can effectively lower glucose levels [173]. The smart insulin patch is made up of glucose-responsive vesicles, consisting of hypoxia-sensitive hyaluronic acid, loaded with insulin and glucose oxidase enzyme [174]. Hypoxia caused by the oxidation of glucose in the hyperglycaemic state promotes the reduction of hyaluronic acid that triggers the dissociation of vesicles and the release of insulin [174]. This patch has been shown to be effective at regulating glycaemia *in vivo* [174]. Other similar patches, bearing microneedles loaded with insulin and a non-degradable glucose-responsive polymeric matrix, have also proven to function well in mice and swine [175]. Although these glucose-responsive insulin systems are in their infancy in terms of development, they represent promising areas of research towards the functional replacement of the pancreatic β cell.

Conclusion

It is clear that technologies for insulin administration have significantly progressed since the first insulin pen was released over 35 years ago. The development of new technologies facilitates the move towards a more personalized care paradigm, as healthcare professionals can now tailor treatment options to suit the individual needs of the person with type 1 diabetes. Although not without their limitations, insulin pumps reduce hypoglycaemia, modestly improve glycaemic levels, and have positive impacts on quality of life in a number of groups of people with type 1 diabetes. As insulin pump technology continues to evolve, the benefits in these domains are expected in increase, thereby easing the day-to-day burden of diabetes self-management. Identifying which cohorts of people with type 1 diabetes derive the most benefit from advanced diabetes technologies is critical to ensure optimum utilization of healthcare resources. However, if long-term cost-effectiveness can be established, integrated automated insulin delivery systems may well become the standard of care for type 1 diabetes over time.

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34 Whole Pancreas and Islet Cell Transplantation

Braulio A. Marfil-Garza[1], Peter A. Senior[2,3], and A.M. James Shapiro[2]

[1] Department of Surgery, University of Alberta, Edmonton, Alberta, Canada
[2] Department of Medicine, University of Alberta, Edmonton, Alberta, Canada
[3] Clinical Islet Transplant Program, University of Alberta, Edmonton, Alberta, Canada

Key points

- Whole pancreas and islet cell transplantation are robust and safe options for people with type 1 diabetes and persistent problematic hypoglycaemia.
- Whole pancreas and islet cell transplantation improve patient survival and have positive impacts on diabetes-related complications by stabilizing the progression of macro- and microvascular complications.
- Whole pancreas transplantation is associated with higher rates and longer duration of insulin independence compared to islet cell transplantation.
- Whole pancreas and islet cell transplantation provide optimal glycaemic management post-transplant and near complete abrogation of severe hypoglycaemia.
- In islet cell transplantation, graft function is preserved for several years beyond the loss of insulin independence, which results in better glycaemic levels over time.
- Despite improving success with current β-cell replacement therapies, many issues remain, including limited organ/tissue source, challenges with peri-procedural care, and the need for lifelong immunosuppression.

What is the problem?

Diabetes care has undergone one of the most notable revolutions in the history of medicine. Over the last 100 years since the discovery of insulin, our paradigm has evolved from saving lives to optimizing treatment for people with diabetes. Realization that intensive glycaemic management ameliorates the progression of diabetes-related complications in people with both type 1 diabetes (Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications cohorts) [1,2] and type 2 diabetes (UK Prospective Diabetes Study) [3] prompted efforts to establish rigorous glycaemic targets (glycated haemoglobin [HbA_{1c}] levels ≤7%; 53 mmol/mol), which are now advocated for most non-pregnant adults with diabetes [4,5]. While the implications of these targets have been debated, particularly in relation to important patient-related outcomes (e.g. end-stage renal disease, ESRD) [6], optimal glycaemic management remains one of the maxims in diabetes care. This fact has changed the natural history of diabetes and transformed its epidemiological picture. Chronic manifestations of the disease such as nephropathy, neuropathy, or vascular disease have become more common and now occupy a more prominent space in clinical guidelines.

Unfortunately, striving for optimal glycaemic levels is challenging, particularly in type 1 diabetes. Iatrogenic hypoglycaemia is particularly relevant and one of the most consistently reported adverse effects with intensive insulin treatment. Early clinical trials reported a 2–6-fold increase in the incidence of severe hypoglycaemic episodes [2,3,7], with more than half of these occurring during sleep [7]. An incidence of ~50% in individuals with type 1 diabetes [8] supports the generalized perception that severe hypoglycaemia is limited to type 1 diabetes. However, a meta-analysis reporting a prevalence of severe hypoglycaemic episodes of 23% in individuals with type 2 diabetes treated with insulin [9] highlights the relevance of this issue in both populations. The global burden of hypoglycaemia-related mortality is equally worrisome. While catastrophic scenarios such as *death-in-bed syndrome* remain uncommon [10], a study using the World Health Organization (WHO) mortality database reports a standardized overall proportion of 4.49 deaths due to hypoglycaemia per 1000 total diabetes deaths (range 0.11–283.1) [11]. This makes hypoglycaemia a key barrier for optimal glycaemic management [12].

Despite these numbers, hypoglycaemia remains a relatively neglected complication [13]. It is noteworthy that the 2021 American Diabetes Association's Standards of Care now include a time in range of >70% and below range of <4% when using ambulatory glucose profiles as a key glycaemic goal [5]. This will raise awareness of the importance of addressing glycaemic variability. However, problematic hypoglycaemia (defined as ≥2 episodes of severe hypoglycaemia per year or 1 episode + hypoglycaemia unawareness, extreme glycaemic lability, or maladaptive behaviour) demands more individualized management. Current recommendations propose a four-stage tiered algorithm:

1. Structured or hypoglycaemic-specific education programmes.
2. Continuous subcutaneous insulin infusion or continuous glucose monitoring.

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3. Sensor-augmented insulin pumps and/or very frequent contact with a specialized hypoglycaemia service.
4. β-cell replacement therapies with either whole pancreas or islet cell transplantation [14].

While β-cell replacement therapies are the last resource, they effectively address the problem; both forms abrogate problematic hypoglycaemia in nearly all individuals while providing optimal glycaemic levels. In this chapter, we will describe whole pancreas and islet cell transplantation, dissect the current clinical evidence, explore the main challenges ahead, and present some potential solutions.

β-cell replacement therapies: a potential solution for diabetes

β-cell replacement therapies are robust alternatives to treat difficult-to-manage diabetes and problematic hypoglycaemia that persists despite conventional therapies. They have undergone significant refinements, and outcomes have improved substantially since their inception. Figure 34.1 depicts the growth of research in the field and provides historical context. Before the discovery of insulin, a relationship between the pancreas and diabetes, which was first identified by Von Mering and Minkowski in 1892, had already driven several attempts to reverse diabetes through pancreatic tissue transplantation [15]. British surgeons Watson-Williams and Harsant performed the first transplant of fragmented sheep pancreatic tissue to a 13-year-old child with diabetic ketoacidosis in 1894; James Allan followed with xenografts composed of feline pancreatic fragments in another person with diabetes [16]. Charles Pybus was the first to transplant human cadaveric fragmented pancreatic tissue into the subcutaneous space of two male individuals with diabetes in 1916 [17]. Repeated failure to achieve normoglycaemia, likely due to prompt immune rejection (the basis of transplantation immunology was not established until the 1950s), coupled with success with contemporary insulin therapies, led to abandonment of β-cell replacement therapies for a few decades. It was not until the 1960s, when the use of steroids and new immunosuppressants allowed successful renal transplantation, that the interest in both whole pancreas and islet cell transplantation was reinvigorated.

Whole pancreas transplantation

History

Whole pancreas transplantation was first conceived as a complementary procedure to improve the clinical success of kidney transplantation in individuals with ESRD secondary to diabetes. In 1966, Drs Kelly and Lillehei performed the first simultaneous segmental pancreas–kidney transplant on a person with type 1 diabetes at the University of Minnesota. This first attempt allowed complete insulin independence for six days before insulin resistance (probably due to high doses of steroids) and graft pancreatitis (probably due to pancreatic duct ligation) ensued. The patient died two weeks after pancreatectomy from a pulmonary embolism [18]. The second simultaneous pancreas–kidney (SPK) transplant, performed by Dr Lillehei, comprised a pancreaticoduodenal transplant (whole pancreas) with a cutaneous duodenostomy to manage exocrine drainage [19]. Subsequently, iterations of the surgical technique by Drs Lillehei, Lárgiader, and Idezuki, such as enteric drainage through a Roux-en-Y duodenal jejunostomy, enabled graft survival for up to one year post-transplant [19]. Other attempts at whole pancreas transplantation, mostly SPK, were done in the USA, Europe, and South America; however, success was minimal. Only one individual from Dr Lillehei's series of 25 cases reported up to 1970s maintained function for one year post-transplant [20]. Ureteral exocrine drainage, pioneered by Gliedman and colleagues in the early 1970s, improved graft survival (up to 50 months); however, this was ultimately abandoned due to anastomotic leakage [21].

In the 1970s–1980s, segmental pancreatic transplantation was revisited, with two techniques to manage exocrine drainage showing improved outcomes, the open drainage (into the peritoneal cavity) and duct polymer injection. The former, as reported by Dr Sutherland et al. from the University of Minnesota, allowed insulin independence for 18 years; however, some transplant recipients suffered from peritonitis and/or pancreatic ascites [22]. Segmental pancreatic transplantation was later coupled with bladder drainage, pioneered by Dr Sollinger from the University of Wisconsin, which became a very common technique during the 1980s due to the low incidence of complications and the added benefit of offering a non-invasive method to monitor for rejection [23]. Later modifications of this technique, such as duodeno-cystostomy, implemented as part of a whole pancreatic transplantation procedure, became popular in the late 1980s; nearly 90% of pancreatic transplantation had bladder drainage during that period. However, a high incidence of urinary tract infections, reflux pancreatitis, and metabolic abnormalities (e.g. acidosis) demanded surgical conversion to enteric drainage in many cases, which led to a relative abandonment of this technique [20].

Enteric drainage is now the preferred approach, with as many as 90% of whole pancreatic transplants having enteric exocrine drainage [24]. Venous drainage is an interesting issue. To replicate physiology, portal drainage was initially explored. However, it was not widely adopted, and because of technical complexity and no clear metabolic benefits, only ~8–20% of transplant are managed with this approach currently [24]; most individuals undergo systemic venous drainage to the common and/or external iliac vessels or the distal vena cava.

Following relative standardization of the surgical techniques, the issue of immunosuppression became central for long-term clinical success. Professor Sir Roy Calne and colleagues first reported the use of cyclosporine A as a successful agent for immunosuppression following whole pancreatic transplantation. He was also the first to describe portal vein drainage in pancreatic transplantation. Combination with steroids was advocated by Dr Starzl's group to reduce cyclosporine A–induced nephrotoxicity; triple therapy with cyclosporine A, steroids, and azathioprine was later introduced by Dr Sutherland's group [20]. Successful clinical trials with tacrolimus by Dr Starzl led to its widespread use as maintenance immunosuppression [20]. In the mid-1990s, mycophenolate mofetil (MMF) was then introduced [24]. Induction immunosuppression regimens involving T-cell depletion, such as anti-thymocyte globulin (ATG), and steroids were introduced in the late 1990s to prevent early rejection.

Procedural considerations

Today, the typical whole pancreas transplant occurs in a person with type 1 diabetes (~90%), older than 30 years (~90%), with ESRD, and comprises an SPK (~84%) with enteric exocrine (91–92%) and systemic venous (~80%) drainage [24]. Whole pancreas transplantation is a major surgery demanding expertise in

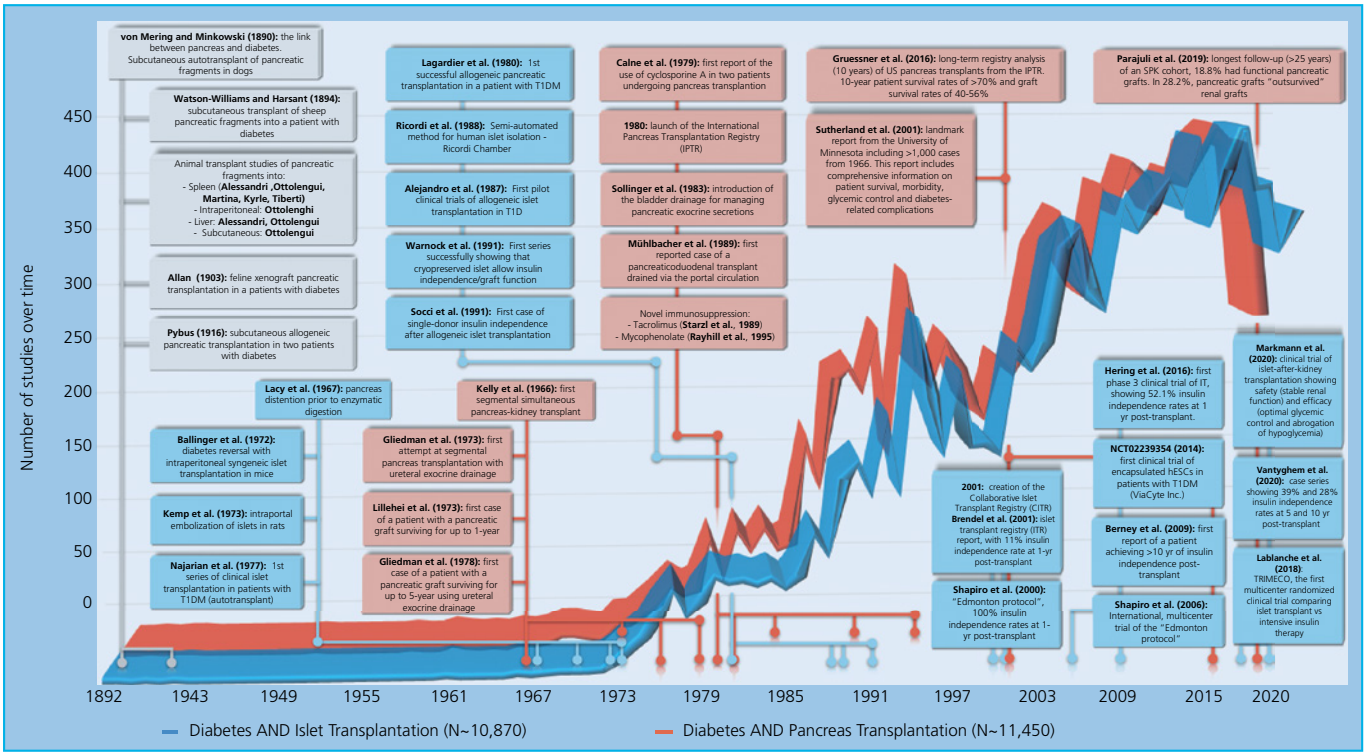

Figure 34.1 Growth of the field and a timeline to clinical success. A non-systematic search in PubMed for publications using the terms (islet transplant* OR pancreas transplant*) AND diabet* up to 1 January 2021. Additionally, we included several key historical studies, despite their not appearing in the original search, due to their relevance.

perioperative management, thus >70% of the transplants are done in high-volume centres. Donor selection is a key consideration for a successful whole pancreas transplantation. The *ideal* pancreatic graft would come from a young (<50 years old) and lean (normal body mass index, BMI) donor.

A detailed description of the surgical technique is beyond the scope of this chapter, but several considerations are worth highlighting. Whole pancreas transplantation carries the greatest risk of graft thrombosis among abdominal transplants, which is the most common cause of early graft loss (5–10%). Thus, careful consideration of surgical aspects such as optimal vessel mobilization (i.e. use of atraumatic vascular clamps, proper length venotomy and arteriotomy, proper suture technique) and flexibility to choose the optimal site of vascular anastomosis are all important details. Importantly, while systemic anastomosis is the preferred method for venous drainage (largely due to less complex dissection being required), the jury is still out on the superior metabolic and potential immunological benefits of the portal venous drainage approach [25].

A final comment concerns immunosuppression. Compared to islet cell transplantation, T-cell–depleting agents (i.e. ATG) are the most commonly used agents for induction immunosuppression in whole pancreas transplantation (68% of cases) [24]. Stronger, more specific, and more expensive immunosuppressants, such as basiliximab or alemtuzumab, have not consistently shown clinical benefit when compared (even in a randomized fashion) with ATG [26]. For maintenance immunosuppression, the preferred regimen comprises tacrolimus, MMF, and prednisone (± tapering/withdrawal); however, a shift towards steroid-free immunosuppression has been advocated recently, particularly by high-volume centres [24]. This practice remains controversial, as a consistent clinical benefit has not been observed [27].

Indications

Most whole pancreas recipients have type 1 diabetes, but this procedure has also been undertaken in individuals with type 2 diabetes. There are three main types of whole pancreas transplantation: simultaneous pancreas–kidney (SPK), pancreas-after-kidney (PAK), and pancreas-alone (PTA) transplants. Hence, some of the indications, although overlapping, may differ with each of these procedures (Table 34.1). In broad terms, SPK is recommended for individuals with severe diabetes and ESRD (estimated glomerular filtration rate [eGFR] <20 ml/min/1.73 m^2); PAK is usually recommended as a sequential procedure when recipients of a kidney transplant have a viable living kidney donor identified, but a deceased pancreas has not been identified; PTA is recommended for individuals that have frequent, acute, and severe complications of diabetes, such as ketoacidosis and hypoglycaemia with or without hypoglycaemia unawareness [28].

Table 34.1 Indications and contraindications for β-cell replacement therapies.

Indications
People with type 1 diabetes (typically with duration >5 yr)
People with type 2 diabetes may be candidates for a whole pancreas transplantation if they have the following conditions:
• Low exogenous insulin requirement
• BMI <30 kg/m^2
HbA_{1c} >7.5–8.0% (58–64 mmol/mol) despite expert diabetes management (including endocrinologist/diabetologist and diabetes educators)
Problematic hypoglycaemia (≥2 episodes/yr of severe hypoglycaemia) despite optimal diabetes management with insulin pump and adequate monitoring by an endocrinologist/diabetologist and diabetes educators
At least one episode of severe hypoglycaemia in the past year, defined as blood glucose <54 mg/dl (3 mmol/l) plus one of the following symptoms: memory loss, confusion, behavioural changes, impaired consciousness, seizure, or visual symptoms, in which the person was unable to treat themselves and which resolved after carbohydrate intake or glucagon administration.
Evidence of impaired awareness of hypoglycaemia and/or extreme glycaemic lability using objective scores, such as the Clarke score (≥4), HYPO score (≥1000), or lability index (≥400), among others.
A composite of Clarke score ≥4 + HYPO score ≥75th percentile (≥423) + lability index ≥75th percentile (≥329) may also be used
Major fear of maladaptive behaviour related to hypoglycaemia may also be considered
Recurrent episodes of diabetic ketoacidosis and/or severe, rapidly progressing complications of diabetes may also be considered
Candidates for either a simultaneous pancreas–kidney or islet–kidney transplant should meet criteria for a kidney transplant alone
Contraindications
Age >60 yr
This is an absolute contraindication for whole pancreas transplantation and a relative contraindication for islet cell transplantation
BMI >30 kg/m^2 (28 kg/m^2 may be preferred for whole pancreas transplantation)
Insulin requirements >1.0 U/kg/d or HbA_{1c} >10.0% (86 mmol/mol)
High insulin requirements and/or HbA_{1c} levels are not a contraindication for whole pancreas transplantation
Untreated proliferative retinopathy
High cardiovascular risk (threshold for a prohibitive cardiovascular risk may be lower for whole pancreas transplantation)
• Uncontrolled hypertension
• Myocardial infarction within 6 mo
• Evidence of ischaemia on functional cardiac testing in the previous year
• Left ventricular ejection fraction <30%
History of malignancy
• Completely resected squamous or basal cell carcinoma of the skin is not a contraindication
Untreated infection (including viral infections, such as hepatitis B or C and HIV)
• History of opportunistic infections such as aspergillus, histoplasmosis, or coccidioidomycosis in the previous year
Inability to comply with immunosuppression and proper follow-up
Any medical (including psychiatric) condition that could interfere with safe participation and follow-up post-transplant

BMI, body mass index; HbA_{1c}, glycated haemoglobin.
Source: Adapted from Samoylova et al. 2019 [28], Wojtusciszyn et al. 2019 [29], Rickels et al. 2018 [30], and Dajani and Shapiro 2019 [31].

Islet cell transplantation

History

In the early 1960s, Dr Paul Lacy and his team at the Washington University School of Medicine inaugurated the modern era of islet transplant research by championing a paradigm shift in the field: separation of the endocrine and exocrine components of the pancreas and islet purification. Building on early ideas from Leonid W. Sobolew and the pioneering works of Drs Hellerström and Moskalewski using manual pancreatic dissection [32] and the use of collagenase [33], respectively, Dr Lacy's team introduced the two-step islet isolation process using intraductal pancreatic distention to dissociate the tissue and islet purification using discontinuous density gradients (e.g. Ficoll®, Pharmacia & Upjohn, Kalamazoo,

MI, USA) [16]. This became the gold standard for rodent islet isolation. Having access to pure and functional islets led to successful transplantation studies and diabetes reversal in murine models [34]. The conditions for the first clinical trials were met when Drs Kemp and Lacy established the superiority of intraportal (compared to intraperitoneal) infusion for islet cell transplantation [35]; this remains the gold standard in the clinic [36].

In the late 1970s, Dr John Najarian and colleagues at the University of Minnesota were the first to demonstrate that insulin independence could be achieved with intraportal islet infusion (auto-transplantation) [37, 38]. In 1980, Drs Largiadèr, Kolb, and Binswanger at Zurich University reported the first case of insulin independence (~10 months) in an individual with diabetes following allotransplantation of pancreatic microfragments (~200 000 islets) into the spleen [39]. Subsequent clinical success was hampered by impure islet preparations and suboptimal immunosuppression, which led to infusion of low islet masses and complications (e.g. thrombosis) and prompt immune rejection [40]. Thus, islet isolation techniques were revisited. Intraductal collagenase perfusion of the pancreas, coupled with gentle mechanical dissociation and density gradient purification, was introduced by Drs Warnock, Rajotte, and colleagues at the University of Alberta [41, 42]. This approach yielded high-purity islet preparations (>90%) and enabled high rates of post-transplant normoglycaemia after a single-donor islet transplant in dogs [41]. Shortly thereafter, these researchers reported on a 36-year-old person with type 1 diabetes who achieved sustained (at least five months) insulin independence after receiving an islet graft composed of both fresh and cryopreserved islets with 75% purity; such purity enabled high doses (>10 000 islets/kg) without any complications [43, 44].

The biggest breakthrough came with the introduction of the *automated* method for islet isolation, designed and implemented by Dr Camillo Ricordi while working in Dr Lacy's laboratory. As stated in his 1988 paper [45], the automated method met the following requirements:

1. Minimal traumatic action on the islets.
2. Continuous digestion in which the islets that are progressively liberated can be saved from further enzymatic action.
3. Minimal human intervention in the digestion process.
4. High yield and purity of the isolated islets.

This method swiftly became the standard for human islet isolation all over the world. A few years later, Dr Scharp and colleagues reported on the first person with type 1 diabetes achieving transient insulin independence using the automated method [46]. The same year, a case series of six individuals with type 1 diabetes treated with islet cell transplantation using the automated method for islet isolation was reported by Dr Socci and colleagues from the San Raffaele Institute of Milan, Italy. Notably, this series included the first person to achieve transient insulin independence after islet cell transplantation from a single donor [47]. Further additions to islet isolation protocols included semi-automated density gradient separation using the Cobe® IBM 2991 cell separator (IBM Systems Development Division, Endicott, NY, USA) by Lake et al. [48], cold preservation solutions by Olack et al. [49], and techniques for islet staining by Latif et al. [50], which ultimately led to standardization of reporting on islet preparations (i.e. numbers, mass, viability, etc.), which was greatly required to allow meaningful comparisons of results between centres [51]. While optimization of the islet isolation process remains an ongoing effort in the field, advances up to now have enabled infusion of pure and large islet masses (up to 1 000 000 islets). However, the lack of long-term clinical success in the late 1990s shifted the focus towards improving immunosuppression and peri-transplant care.

In 1997, Secchi et al. reported that induction immunosuppression with steroids and ATG, coupled with maintenance immunosuppression using azathioprine, cyclosporine A, and steroids, as well as peri-transplant use of insulin, allowed insulin independence rates of 35% after intraportal islet cell transplantation in individuals with 'insulin-dependent diabetes mellitus' [52]. Researchers at the University of Miami, using OKT3 (anti-CD3) as induction agent (instead of ATG), reported graft survival rates of up to six years post-transplant in two of six individuals [53]. Unfortunately, by the end of the 1990s, the global clinical experience was not encouraging. By 2000, the Islet Transplant Registry, which included information on 237 allotransplants, reported a one-year insulin independence rate of 11% [54]. Importantly, a milestone in the field was achieved that year with the Edmonton Protocol, carried forward by a team led by James Shapiro at the University of Alberta. By using large numbers of fresh islets (>11 000 islet equivalents [IEQ]/kg) and a steroid-free immunosuppression regimen based on daclizumab (anti-interleukin [IL]-2 antibody), sirolimus, and tacrolimus, this protocol was the first to achieve 100% one-year insulin independence rates in seven consecutive non-uraemic individuals with type 1 diabetes [55]. The Edmonton Protocol reinvigorated research in the field, inaugurated the new era of islet cell transplantation, and motivated many countries to start islet cell transplantation programmes. Clinical outcomes after the Edmonton Protocol will be discussed later.

Procedural considerations

The pathway towards a successful islet cell transplantation differs when compared to whole pancreas transplantation and other organs. In addition to obtaining a viable organ, islet cell transplantation requires pancreas processing and islet isolation. This process is done by tissue specialists at dedicated facilities, following good manufacturing practices (Figure 34.2) [57]. Importantly, the efficiency and success of islet isolation (adequate number, quality, purity, viability) are variable and heavily dependent on the skills of the isolation team. Following islet isolation, suitable preparations are infused into the intraportal circulation of the recipient through percutaneous transhepatic access. This procedure is typically done using procedural sedation and through fluoroscopic guidance by interventional radiologists. After confirming proper positioning of the catheter with a portal venogram, the islets are infused using a closed gravity-fed bag [58]. The use of heparin to prevent the instant blood-mediated inflammatory response and portal vein thrombosis together with a peri-transplant insulin infusion to maintain euglycaemia and promote β-cell *rest* following transplantation is a key component of most islet cell transplantation protocols [59]. These interventions are modified to subcutaneous low molecular-weight heparin and aspirin, as well as subcutaneous insulin, 48 hours after transplant.

In terms of immunosuppression, the original Edmonton Protocol has been modified in many centres around the world, including the Edmonton site itself. Current induction immunosuppression either uses agents to prevent activation of lymphocytes – anti-CD25 (IL-2 receptor α-chain) blockers such as daclizumab, basiliximab – or lymphodepletion agents – ATG (horse or rabbit derived), anti-CD52 blockers (alemtuzumab) – or anti-CD3 blockers (OKT3, teplizumab); some centres include steroids in their induction immunosuppression regimens. These are usually combined with

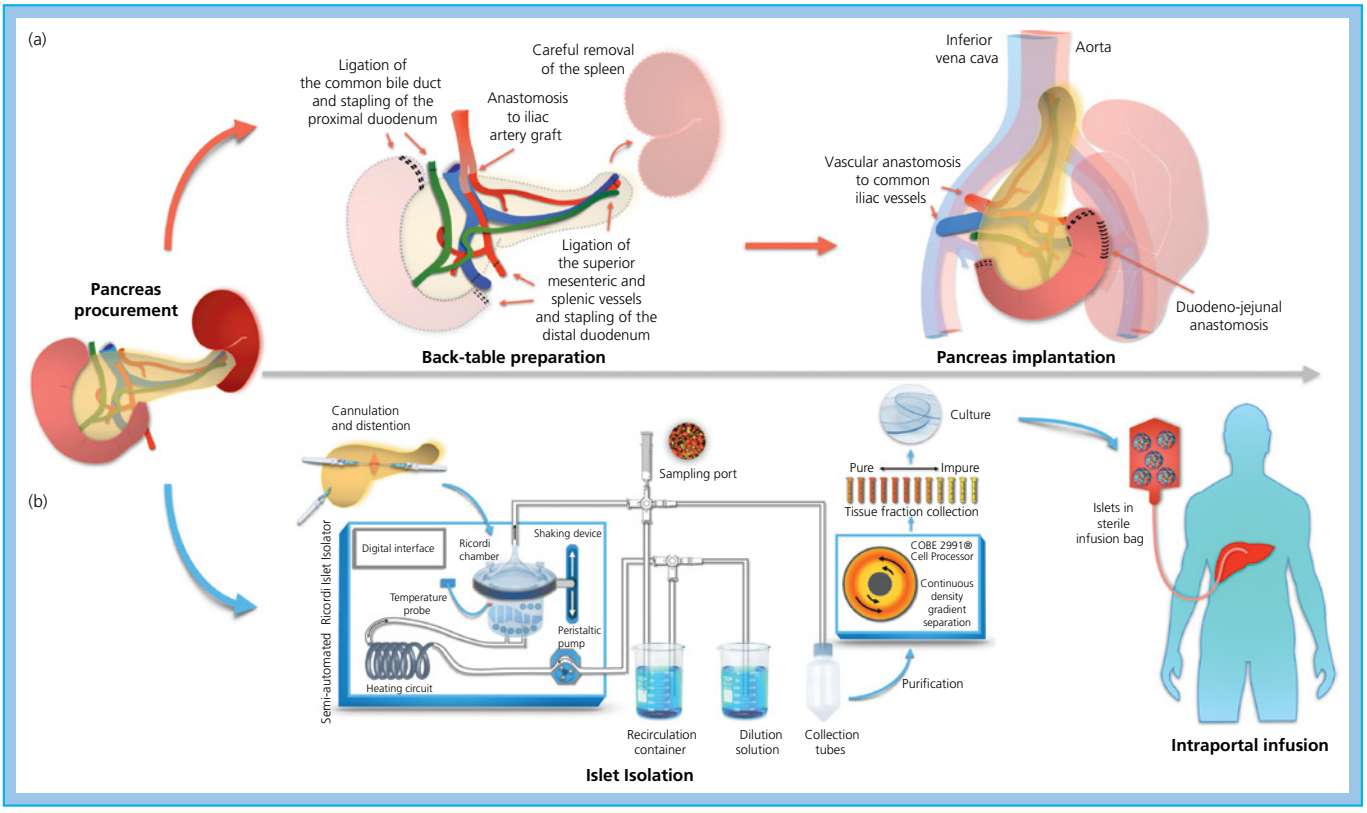

Figure 34.2 Pancreas and islet cell transplantation procedures. (a) Pancreas transplantation. The pancreas graft is removed *en bloc* with the duodenum and spleen to prevent injury to the proximal and distal pancreas. During cold-phase dissection, the portal and superior mesenteric veins, as well as the gastroduodenal, splenic, and superior mesenteric arteries, are carefully identified, ligated, and divided individually. During back-table preparation, the spleen, peri-pancreatic tissue, and fat are removed carefully to avoid parenchymal injury to the pancreas. The duodenal segment is shortened by stapling proximally and distally. The splenic and superior mesenteric vessels are ligated, as well as the common bile duct. Vascular reconstruction is performed with the donor iliac artery bifurcation as a Y-graft to provide single inflow to the splenic and superior mesenteric arteries. No extension graft is used for the portal vein due to a higher risk of thrombosis. Integrity of the vascular arcade is tested with fluid flush. The prepared graft is implanted in the right iliac fossa. The diagram shows vascular anastomosis to the common iliac vessels and a duodeno-jejunal anastomosis for exocrine drainage, but these may vary by centre. (b) Islet cell transplantation. Islet isolation starts with processing of the resected pancreas (i.e. resection of the spleen, duodenum, and peri-pancreatic fat). Following exposure through an incision of the pancreas mid-body, the main pancreatic duct is cannulated with two catheters, directed at the head and tail of the pancreas; flow through the major papilla is blocked with a third catheter. Distention of the pancreas is achieved by infusing cold collagenase through the catheters using a perfusion machine. After distention, the pancreas is sliced and introduced in the Ricordi chamber for enzymatic and mechanical digestion. Enzymatic digestion is achieved by activating the collagenase (warming to ~36 °C); mechanical digestion occurs by introducing silicon nitride/metal marbles inside the chamber and shaking of the chamber. The solution is recirculated until the pancreas is appropriately digested, which is assessed by taking samples at different time points and staining them with the zinc-binding dye dithizone. When deemed appropriate, the solution is diluted to stop enzymatic activity and the tissue is then purified using a cell processor and continuous density gradient centrifugation. The purest tissue fractions are harvested for culture and, subsequently, transplantation. Source: The islet isolation diagram is modified from Marfil-Garza et al., 2021 [56].

anti-inflammatory agents such as tumour necrosis factor (TNF)-α (etanercept, infliximab) and/or IL-1 (anakinra) inhibitors [60]. Current maintenance immunosuppression regimens include combinations of calcineurin inhibitors (tacrolimus, cyclosporine A), mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus), and/or MMF. Strategies to improve islet survival, engraftment, and avoid immune rejection will be discussed later.

Indications

Lifelong immunosuppression post-transplant has been associated with toxicity and adverse effects, such as opportunistic infections and neoplasms. Arguably, this issue represents the major limitation for the generalized use of islet cell transplantation in every person with diabetes. Thus, in its current state, islet cell transplantation is limited to individuals with type 1 diabetes suffering from refractory problematic hypoglycaemia and/or impaired awareness of hypoglycaemia [14], in which the perceived benefits for quality of life [61] and survival [62], compared to no transplant, outweigh the risks related to the procedure and lifelong immunosuppression. For those with functioning renal transplants, already committed to lifelong immunosuppression, the risk–benefit ratio is simpler. Regarding selection of the individual, recent recommendations by the TREPID working group and the International Pancreas and Islet Transplant Association (IPITA)/European Pancreas and Islet Transplant Association (EPITA) opinion leader workshop include accounting for physiological age, weight, cardiovascular risk, the presence of diabetes-related chronic complications, previous organ transplantation (and sensitization state), current use of immunosuppression, and, importantly, the person's capacity to deal with hypoglycaemia [29,30].

A synthesis of current indications and contraindications for islet cell transplantation is presented in Table 34.1. It should be emphasized that specific instruments to assess severity of hypoglycaemia, glycaemic lability, and impaired awareness of hypoglycaemia, such as the HYPO score [63], lability index, glucose coefficient of variation, and Clarke and Gold scores [64], may help to complement clinical assessment and decide on eligibility for islet cell or whole pancreas transplantation and to define appropriate patient-centred outcomes and realistic expectations [30]. However, they should not represent the main and only strategy for selection of individuals.

Clinical outcomes: state of the art

Whole pancreas transplantation

Survival and morbidity

Advances in surgical techniques, peri-transplant care, and immunosuppression have improved patient survival and decreased morbidity following whole pancreas transplantation. Currently, the three-year survival rate of SPK, PAK, and PTA is 95%, 93%, and 96%, respectively [24]. Reports with longer follow-up show a 10-year survival rate of ~76%, ~72%, and ~82% for SPK, PAK, and PTA, respectively [65]. Interestingly, while it is clear that SPK confers a survival benefit when compared to remaining on the waiting list [66–69] or to kidney transplant alone (living or deceased donor) [70], there is controversy over PAK and PTA.

Studies looking at the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR) databases found no overall survival benefit following PAK compared to remaining on the waiting list; however, restricting the analysis to follow-up beyond one year showed a benefit for survival (hazard ratio [HR] 0.18, 95% confidence interval [CI] 0.13–0.25) [68]. In contrast, a more recent study found that PAK conferred no survival benefit at 5–10 years (HR 1.07, 95% CI 0.84–1.37) [67]. For PTA, the same report with UNOS/IPTR data found no overall benefit for survival, however, restricting the analysis to follow-up beyond one year showed a survival benefit (mortality HR 0.15, 95% CI 0.08–0.29) [68]. One study showed that PTA added 2.4 life-years compared to remaining on the waiting list [69]. Conversely, more recent studies have shown no survival benefit with PTA [71]. Importantly, specific analysis considering pancreatic graft status in both PAK and PTA populations was not done with these studies and is needed, as there is evidence from the SPK population that benefits for survival seem to be conditional on pancreatic and kidney graft survival [24,70]; naturally, kidney graft survival may be more strongly associated with survival rate [24,72].

Studies showing improvement in average life-years saved and quality-adjusted life-years using probabilistic simulation models [73] strengthen the case for SPK in individuals with severe diabetes and ESRD as a more cost-effective strategy compared to kidney transplant alone. Finally, the decision to move forward with whole pancreas transplantation should be weighed against the higher 90-day post-transplant mortality rates for all pancreas transplantation categories, compared to individuals on the waiting list [67].

Glycaemic management and graft survival

Currently, the three-year pancreatic graft survival rates are 86.9%, 78.8%, and 74.0% for SPK, PAK, and PAT, respectively [24]. Reports with longer follow-up show a 10-year pancreatic graft survival of ~55%, ~38%, and ~35% for SPK, PAK, and PTA, respectively [65]. These numbers are somewhat representative of the rates of insulin independence post-transplant, given that one of the definitions for graft failure in whole pancreas transplantation includes a return to insulin. Thus, considering that individuals are insulin independent, optimal glycaemic levels as well as complete abrogation of severe hypoglycaemic episodes are expected as long as the pancreatic graft is surviving. Indeed, people with a failed pancreatic graft seem to *lose* all benefit in terms of glycaemic indices and incidence of symptomatic hypoglycaemia [74]. Interestingly, impaired glucose tolerance may be observed after 10 years of follow-up in ~50% of cases, even when only evaluating *functional* pancreatic grafts [75]; the clinical impact of these findings (i.e. diabetes-related complications) remains unknown.

Several risk factors may correlate with graft failure, such as low-volume centre, older age, BMI >30 kg/m^2, use of dialysis pre-transplant, enteric drainage, immunological status pre-transplant (panel reactive antibodies [PRA] >20%), non-depleting induction immunosuppression, and the use of maintenance immunosuppression regimens other than tacrolimus + MMF + steroids [24,76]. The duration of diabetes is also a determinant of graft survival, with slightly better rates of graft survival reported for those with long-standing (>20 years) type 1 diabetes, particularly for persons undergoing SPK [76]. Interestingly, rates of graft survival, as well as glycaemic levels, are similar between people with type 1 diabetes and type 2 diabetes [77]. This, coupled with the fact that whole pancreas transplantation seems to be associated with a low rate of type 1 diabetes recurrence (~7%) [78], suggests that alloimmunity is the predominant determinant of graft survival. However, conversion from a negative to a positive autoantibody status possibly confers a

lower probability of graft survival over time [79]. Currently, the benefits of monitoring either allo- and autoantibody status post-transplant are not clearly established.

Diabetes-related complications

Retinopathy

Early reports comparing successful to failed whole pancreas transplants showed no difference in progression of retinopathy, for both PTA [80] and SPK [81,82]. Importantly, most individuals had previous laser photocoagulation and their degree of retinopathy remained stable. Later, a study comparing successful SPK to failed SPK or kidney transplant alone showed improvement in visual acuity and stabilization of retinopathy in the former group for up to three years of follow-up [83]. Although ~80% of the individuals had laser photocoagulation before transplant, the need for further laser therapy was decreased in the successful SPK group versus the failed SPK or kidney transplant alone group [83]. When compared to conventional insulin therapy, PTA seems to ameliorate progression and/or improve retinopathy in people with non-proliferative retinopathy and stabilize progression in those with proliferative retinopathy [84]; however, the benefits on stabilization of proliferative retinopathy seem to be more pronounced in the SPK population [85].

A recent large study looking at retinopathy after whole pancreas transplantation (mean follow-up of 4.2 years) suggests that, in almost 80% of cases, retinopathy remains stable. Interestingly, 92% of those who progressed did so within one year post-transplant (early worsening) [86]. These authors identified baseline degree of retinopathy, recent (<1 year) treatment with photocoagulation, and PTA as risk factors for early worsening [86]. Another recent study looking at individuals who underwent SPK and had a surviving graft for >25 years reported stabilization of retinopathy in 90 of the individuals, but there was comparative analysis with individuals with a failed graft [87]. Importantly, most individuals undergo whole pancreas transplantation late in the course of their disease have some degree of retinopathy at the time of transplant (~90–100%) and the majority have laser-treated and/or proliferative retinopathy [84,86]. Initially close and then ongoing monitoring of retinopathy after transplant seems prudent, since the benefit of whole pancreas transplantation may be more related to stabilization rather than improvement or reversal of retinopathy, particularly for individuals with proliferative retinopathy.

Neuropathy

Up to 80–100% of people undergoing whole pancreas transplantation have signs of peripheral neuropathy [22,88,89]. However, neuropathy after whole pancreas transplantation has been relatively understudied and, overall, there is a lack of recent reports [22]. A study comparing people with successful versus failed SPK showed rapid and longlasting recovery of neurophysiological measurements such as nerve conduction velocity and amplitude; however, no significant differences were observed compared to control individuals [88]. The classic reports from the University of Minnesota group, which compared successful whole pancreas transplantation with control groups (including failed whole pancreas transplantation and individuals on the waiting list), showed improvement and/or stabilization in nerve conduction studies in the whole pancreas transplantation group. More importantly, these findings also translated into a *clinical benefit*, which was mainly driven by a lack of deterioration in neurological examination scores compared to controls [89,90]. Studies including people undergoing PTA also showed improvement in neurophysiological measurements and neurological examination scores [91]. Correlation of this latter outcome with patient-important outcomes, such as decreased pain, numbness, or complete sensory loss, remains undetermined and should be explored in the future.

Autonomic neuropathy, which has significant impacts on quality of life, has also been understudied. Several measurements of autonomic neuropathy, such as vasomotor function (e.g. capillary vasoconstriction responses), cardiac function (e.g. heart rate variability), and gastric function (e.g. gastric emptying), have been reported to improve after whole pancreas transplantation compared to kidney transplant alone [92,93]. A recent study on SPK long-term survivors reported improvement or stabilization of gastroparesis in 75% of the individuals [87]. Importantly, improvements in autonomic neuropathy have been correlated with improvement in quality of life [93] and hypoglycaemia symptom recognition [94], albeit more studies would strengthen these notions.

Nephropathy

The combined percentages of SPK (84%) and PAK (8%) somewhat reflect the prevalence of kidney disease in candidates for whole pancreas transplantation [24]. As such, two potential *renal* outcomes post-transplant emerge: kidney graft survival/function and native kidney function. For the first outcome, studies have shown that in individuals undergoing SPK, a surviving pancreatic graft confers a survival benefit for the kidney graft [95]; however, this is only observed when compared to individuals receiving a deceased-donor kidney graft [96]. For those undergoing PAK, a surviving pancreatic graft confers a survival benefit for the kidney graft, even when compared to people receiving a living-donor kidney graft. Interestingly, a living-donor kidney graft also improved the rates of pancreatic graft survival compared to a deceased-donor kidney graft [67].

As for the second outcome, early studies showed that normoglycaemia after successful PTA could reverse histological lesions in established diabetic nephropathy after 10 years of follow-up [97]. Later, studies comparing PTA with intensive insulin therapy showed improvement of proteinuria and no significant changes in creatinine clearance [98], which in the context of immunosuppression constitutes a favourable outcome. A large case series by Boggi et al. confirmed that proteinuria improved after PTA, with 54% of persons with macroalbuminuria at baseline reversing to either microalbuminuria (18%) or normal (36%) [92]. These authors reported that those with an eGFR >90 ml/min had a faster and more pronounced deterioration in renal function (~−4.9 ml/min/yr vs ~−2 ml/min/yr in those with <90 ml/min at baseline, $p < 0.05$), possibly due to correction of hyperfiltration [99]. Regarding onset of ESRD after PTA (i.e. need for dialysis or kidney transplantation), large studies have shown a five-year cumulative incidence of 3.5%, 12.2%, and 26.0% and a 10-year cumulative incidence of 21.8%, 29.9%, and 52.2% in individuals with a baseline eGFR of >90, 89–60, and <60 ml/min/1.73 m^2, respectively [100].

A recent report assessing different cohorts (Joslin Clinic, Finnish Diabetic Nephropathy Study, Steno Diabetes Center Copenhagen, and Institut national de la santé et de la recherche médicale [Inserm]) shows a similar 10-year cumulative incidence of ESRD in non-transplanted people with type 1 diabetes and earlier stages of chronic kidney disease (16.5–31.1%); higher incidence rates with more advanced disease were also observed [101]. However, the effects of PTA on renal function are still debated, and

nephrotoxicity secondary to immunosuppression should be considered. Diabetes is also a risk factor for ESRD post-transplant [102], thus the combination of immunosuppression and diabetes may be particularly harmful. Nevertheless, this remains controversial, as large studies in non-renal solid organ transplants have shown an overall five-year cumulative incidence rate of ESRD as high as 18.1% and 21.3% for liver and intestine transplantation, respectively [102], which compares similarly to PTA. Overall, the decision to proceed with PTA should be weighed against the adverse effects of lifelong immunosuppression, among which nephrotoxicity is central, particularly with calcineurin inhibitors.

Cardiovascular disease

Cardiovascular disease and risk factors are highly prevalent in candidates for a whole pancreas transplant. In a large study, 51.8–79.5% had hypertension, 4.1–4.9% had peripheral vascular disease, 1.9–4.1% had a prior coronary bypass, 3.8–5.4% had a prior coronary intervention, 1.8–2.1% had valvular disease, and 0.8–1.1% had a pulmonary circulation disorder at baseline [103]. SPK has the highest prevalence, followed by PAK and PTA [22]. The prevalence of coronary artery disease observed with coronary angiography is substantially higher (~50–70%) [104–107]. The presence of cardiovascular disease at baseline confers a worse prognosis in terms of person and graft survival [22]; however, studies have shown that whole pancreas transplantation stabilizes and/or improves disease markers such as carotid intima-media thickness [108, 109], left ventricular function [110, 111], low-density lipoprotein (LDL) cholesterol [91, 99], triglycerides [109, 111], inflammatory and prothrombotic factors (i.e. homocysteine, von Willebrand factor, D-dimer, etc.) [109], and endothelial dysfunction [109]. More importantly, the incidence of person-centred outcomes, such as cardiovascular death and/or major adverse cardiovascular events (i.e. fatal or non-fatal myocardial infarction or stroke), is lower in those undergoing whole pancreas transplantation when compared to kidney transplant alone, both deceased donor [111–113] and living donor [114], as well as individuals on the waiting list [111, 113]. The benefit seems to be mostly observed for SPK, and somewhat dependent on pancreatic graft survival [114]. In contrast, the evidence for PAK and PTA in terms of important cardiovascular outcomes is inconclusive [22, 114]. Analyses including graft status in these two latter populations could shed more light on these important matters.

Islet cell transplantation

Survival and morbidity

Islet cell transplantation is one of the safest transplants in terms of person survival. The latest report from the Collaborative Islet Transplant Registry (CITR), which gathers clinical data from allogeneic islet cell transplantation from centres all over the world, reports a five-year survival rate of 98.4% [115]. Single-centre studies have reported a mortality rate of 0.3–1.0% per 100 person-years [116, 117]. While morbidity and transplant-related adverse effects are fairly common, a substantial decrease in serious events related to infusion or immunosuppression has been observed, from ~20.0% in the early eras (1999–2002) to ~7% in most recent eras (2011–2014) [115]. Similar to SPK, studies suggest that a simultaneous islet–kidney transplant (SIK) confers a survival benefit compared to both individuals having a kidney transplant alone and those on the waiting list [62]. Importantly, islet cell transplantation substantially improves health-related quality of life [61, 118]. However, samples have been typically small and more studies including appropriate control groups and sufficient follow-up are needed.

Glycaemic management and graft survival

Initial excitement following the publication of the Edmonton Protocol was subsequently tempered by reports showing that insulin independence was not usually sustainable over time, with only ~10% of individuals maintaining insulin independence beyond five years [119]. Later, an international, multicentre trial of the Edmonton Protocol reported one-year insulin independence rates of only 44% [120], which highlighted the importance of centre experience in islet isolation and peri-transplant care. However, over the last two decades a steady improvement in outcomes related to insulin independence and graft survival has been observed [121]. The most recent CITR report shows five-year insulin independence rates of ~30% [115], and single-centre studies have recently reported 10-year insulin independence rates of 18–28% [116, 122]. More consistent has been the change in insulin use following islet cell transplantation, with a decrease of ~70% at 5 years and ~50% at 10 years [115, 117].

While insulin independence and reductions in insulin use are highly desirable, evaluating the success of islet cell transplantation around this outcome may underestimate clinical benefit, since the primary goal of islet cell transplantation is to address problematic and recurrent hypoglycaemia. Hence, an appropriate measure of its success would be abrogation or minimization of severe hypoglycaemic episodes. This view coincides with a person-centred approach, and recent position statements and workshops have advocated for this outcome to take an equally central place when evaluating the success of islet cell transplantation [29, 30]. In this regard, >90% of individuals have complete abrogation of severe hypoglycaemic episodes at 5 years post-transplant [115], but rates of 80–100% at 10 years post-transplant have also been reported [117, 123]. Similarly, restoration of awareness of hypoglycaemia is an important outcome after islet cell transplantation. This is a key phenomenon occurring in candidates for islet cell transplantation. Unfortunately, there is controversy regarding the extent of recovery in terms of the counter-regulatory hormonal responses and symptom recognition during hypoglycaemia following islet cell transplantation. Early experience showed no improvement in either measure [124]; however, more recent studies have shown significantly improved awareness of hypoglycaemia after islet cell transplantation [125–128]. This should be further studied in the future. Finally, abrogation of hypoglycaemia cannot occur at the expense of glycaemic levels. In this regard, islet cell transplantation is also effective, with composite outcomes, such as absence of severe hypoglycaemic episodes and HbA_{1c} <6.5% (48 mmol/mol) or 7.0% (53 mmol/mol), depending on the study, being reported in 62.5–87.5%, 58.3–71.0%, 35–55%, and 21.9–36.3% at 1, 2, 5, and 10 years, respectively [115, 123, 128–130]. Finally, most studies show a substantial and sustained improvement in glycaemic management [131, 132].

Diabetes-related complications

Retinopathy

Retinopathy is common in individuals undergoing islet cell transplantation, with ~60% having some degree of retinopathy [115]. Most studies report stabilization and/or improvement of retinopathy after transplant. Two studies comparing islet cell transplantation

to intensive insulin therapy have reported no progression of retinopathy, with those with more severe retinopathy being more protected [133, 134]. A case series reports similar outcomes, with one person demonstrating improvement of retinopathy one year post-transplant [135]. Finally, a before versus after study showed an increase in blood flow velocities of central retinal arteries and veins one year post-transplant, although no clinical or person-important outcomes (e.g. the use of laser photocoagulation) were reported [136]. We recommend close ophthalmological follow-up post-transplant, since some people may suffer from vitreous haemorrhage and/or need laser photocoagulation or vitrectomy after islet cell transplantation [119].

Neuropathy

On average, ~30% of persons undergoing islet cell transplantation have peripheral neuropathy [115]. Whether islet cell transplantation has an impact on this outcome remains controversial. Two studies comparing islet cell transplantation to intensive insulin therapy found no signification deterioration of nerve conduction velocities following islet cell transplantation [133, 134], while two other studies showed improvement in nerve conduction velocities through time [135, 136]. One of these latter studies showed decreased expression of advanced glycation end products and their specific receptor in nerves and perineural vessels from skin biopsies of people undergoing islet-after-kidney transplantation (IAK) versus kidney transplantation alone [137]. Finally, a study including 21 individuals undergoing IAK showed no deterioration of motor measurements, as well as improvement in sensory measurements at five years post-transplant [138]. Autonomic neuropathy is present in ~20% of people pre-transplant, but the evidence on the impact of islet cell transplantation on this condition is scarce.

Nephropathy

Evaluation of renal function is common in many clinical reports concerning islet cell transplantation. It should be emphasized that, compared to whole pancreas transplantation, most (~80%) individuals undergoing islet cell transplantation do not have ESRD at baseline [115]. Despite optimal glycaemic management during follow-up, some studies have reported a decline in eGFR following islet cell transplantation. In a previous report from our group, we observed a median rate of decline of 0.39 ml/min/1.73 m^2/month, although with wide inter-person variability. Additionally, the proportion of those with micro- and macroalbuminuria also increased post-transplant [139]. However, more recent studies have reported lower rates of renal function decline (GFR measured by ^{99m}Tc-DTPA) following islet cell transplantation compared to medically treated individuals [133, 134, 140]. A recent study reported no statistically significant reduction of eGFR, even after 10 years of follow-up [117].

These conflicting findings may be explained by differences in immunosuppression regimens and baseline renal function. In this regard, the combination of tacrolimus + sirolimus might be more nephrotoxic than tacrolimus + MMF [133, 134, 140–142]; unfortunately, reports with longer follow-up have introduced some controversy into this notion [117]. Studies directly comparing these two regimens are lacking and further research is needed. Renal function status should be considered in the selection process for islet cell transplantation, and particularly in decisions regarding immunosuppression regimens and post-transplant care.

Cardiovascular disease

While islet cell transplantation may be the preferred treatment modality in individuals with a high burden of cardiovascular disease, the prevalence of coronary artery disease, cerebrovascular disease, and peripheral vascular disease according to the latest CITR report is <10%, <3%, and <5%, respectively [115]. These low numbers might be due to underreporting, since there are studies reporting that ~43% of asymptomatic islet cell transplantation candidates have evidence of coronary artery disease on angiography [143]. Additionally, these low numbers may be driven by the fact that most individuals undergo islet-transplant-alone (ITA), as other studies including SIK individuals show a higher prevalence of coronary heart disease [144, 145]. In general, cardiovascular death rates seem to be lower in individuals with a successful islet cell transplant compared to those with unsuccessful islet cell transplant [146]. Following islet cell transplantation, the incidence of coronary artery disease events does not substantially increase compared to non-transplanted people with type 1 diabetes, with a rate of 11 events per 1000 person-years, which is slightly higher than that of the general type 1 diabetes population (8.9 events per 1000 patient-years) [147].

Although more studies are needed to assess important cardiovascular outcomes following islet cell transplantation, there are reports showing improvements in echocardiographic measures (e.g. ventricular ejection fraction), vascular measures (e.g. intima media thickness), cardiovascular biomarkers (e.g. atrial natriuretic peptide, triglycerides, LDL), as well as haemostatic variables (e.g. prothrombotic factors, platelet function, or ultrastructure) [62, 146, 148, 149].

Whole pancreas and islet cell transplantation: competing or complementary therapies?

It is tempting to compare whole pancreas and islet cell transplantation, but this might not be appropriate. Overall, there are few studies directly comparing these two therapies (Table 34.2). Importantly, although some indications overlap, people undergoing whole pancreas and islet cell transplantation are inherently different. Current reports consistently show that compared to whole pancreas transplantation, those undergoing islet cell transplantation are older and with a longer duration of disease [144, 145, 150–153]. Additionally, studies have found that people undergoing SIK have a higher prevalence of coronary artery disease compared to those undergoing SPK [144, 145], and lower survival rates [145]. These differences might be confounded by indications and contraindications for each treatment (e.g. older persons might not be eligible for whole pancreas transplantation, those having SIK might be too sick for SPK). In contrast, studies focusing on whole pancreas and islet cell transplantation alone have not reported differences in cardiovascular status and/or person survival [150, 152]. In terms of morbidity, there is consistency regarding early mortality (<1 year) and post-transplant complications (e.g. relaparotomy), where whole pancreas transplantation has been associated with a higher frequency of these outcomes (Table 34.2). Regarding insulin independence, there is also controversy. Two studies from a single centre comparing SPK to SIK or IAK report higher rates and longer duration of insulin independence [144, 145]. Conversely, studies evaluating whole pancreas and islet cell transplantation alone show similar rates and duration of insulin independence [151, 152]. Glycaemic indices

Table 34.2 Studies including comparative analysis of whole pancreas vs islet cell transplantation.

Author, year, country	Patients and methods	Main results

Gerber et al., 2008, Switzerland [143]	Retrospective cohort
	Type 1 diabetes with ESRD
	SPK: 25
	• Induction IS: basiliximab
	• Maintenance IS: TAC + MMF
	• Mean age (SD): 39.9 (6.0) yr.
	• Mean duration of diabetes (SD): 30.3 (7.1) yr
	SIK: 13
	• Induction IS: basiliximab
	• Maintenance IS: TAC + MMF
	• Mean age (SD): 52.6 (9.5) yr
	• Mean duration of diabetes (SD): 41.7 (9.1) yr
	• Mean total IEQs/patient (SD): 345070 (137511)
	  ○ Mean number of infusions (SD): 2.2 (1.3)
		SPK
		• Insulin independence: 24 individuals (96%) at 1 yr post-transplant
		• Change in HbA_{1c}: 8.7% ➔ 5.8% (71 mmol/mol ➔ 40 mmol/mol) at 3 yr post-transplant (3 patients had a mean HbA_{1c} of 5.3% [34 mmol/mol] at 5 yr post-transplant)
		• Complications:
		  ○ Overall: 12 individuals (48%) had complications related to the pancreas
		  ○ Laparotomy post-transplant: 10 patients (40%)
		  ○ eGFR (ml/min/1.73 m^2): 10.4 ± 4.1 at baseline ➔ 67.3 ± 12.5 at 3 yr post-transplant
		• Costs: €57 772 ± 30 649 (2008)
		• Median duration of hospitalization (SD): 22 (12) d
		ITA
		• Insulin independence: 4 individuals (31%) at 1 yr post-transplant
		• Change in HbA_{1c}: 8.1% ➔ 5.8% (65 mmol/mol ➔ 40 mmol/mol) at 3 yr post-transplant (5 patients had a mean HbA_{1c} of 6.2% [44 mmol/mol] at 4 yr post-transplant)
		• Complications:
		  ○ Overall: 2 individuals (15%) had complications related to the islets
		  ○ Laparotomy post-transplant: 0 individuals
		  ○ eGFR (ml/min/1.73 m^2): 11.8 ± 6.7 at baseline ➔ 49.6 ± 24.0 at 3 yr post-transplant
		• Costs: €76 227 ± 8966 (2008)
		• Median duration of hospitalization (SD): 18 (7) d (compiled)

Maffi et al., 2011, Italy [149]	Retrospective cohort
	Type 1 diabetes without ESRD
	PTA: 33
	• Induction IS: ATG + MPDN
	• Maintenance IS: TAC + MMF, MMF + CsA
	• Mean age (SD): 37 (8.4) yr
	• Mean duration of diabetes (SD): 20 (8.6) yr
	ITA: 33
	• Induction IS: daclizumab or ATG
	• Maintenance IS: TAC + SRL or SRL + MMF
	• Mean age (SD): 36 (8.6) yr
	• Mean duration of diabetes (SD): 23 (9.9) yr
	• Mean total IEQ/kg (SD): not reported
	  ○ One infusion: 9 (27.3%)
	  ○ Two infusions: 16 (48.4%)
	  ○ Three infusions: 8 (24.2%)
		PTA
		• Insulin independence: 25 individuals (75.7%)
		• Change in HbA_{1c}: not reported
		• Complications:
		  ○ Laparotomy post-transplant: 18 individuals (54.5%)
		  ○ Bleeding: 5 individuals (15.5%)
		  ○ CMV reactivation: 21 individuals (63.6%)
		  ○ Deterioration of renal function: 4 individuals (12.1%), 1 required haemodialysis
		• Median duration of hospitalization (IQR): 19 (16–24) d
		ITA
		• Insulin independence: 19 individuals (57%)
		• Change in HbA_{1c}: not reported
		• Complications:
		  ○ Laparotomy post-transplant: 0 individuals (0%)
		  ○ Bleeding: 12 individuals (36.6%)
		  ○ CMV reactivation: 2 individuals (6.0%)
		  ○ Deterioration of renal function: 5 individuals (15.1%), 2 required haemodialysis
		• Median duration of hospitalization (IQR): 16 (9–19) d (compiled)

Bellin et al., 2012, USA (data from CITR was included) [150]	Retrospective cohort
	• Different cohorts, indirect comparisons with PTA
	Type 1 diabetes without ESRD
	PTA: 1104
	• Induction IS: ATG or alemtuzumab or anti-CD3 or IL-2 receptor antagonists
	• Maintenance IS: TAC or CsA or SRL or MMF
	• Mean age (SD): 33.3 (7.1) yr
	ITA: 269
	• Induction IS: ATG or alemtuzumab or anti-CD3 or IL-2 receptor antagonists
	• Maintenance IS: TAC or CsA or SRL or MMF or efalizumab
	• Mean age (SD): 40.6 (1.4)–45.1 (1.5) yr
	• Cumulative IEQ × 1000 (SD): 614 (46)–908 (87)
	  ○ One infusion: 79 (29.4)
	  ○ Two infusions: 114 (42.3)
	  ○ Three infusions: 72 (26.8)
	  ○ ≥Four infusions: 4 (1.5)
		PTA
		• Insulin independence: 50% at 5 yr
		• Change in HbA_{1c} levels: not reported
		• Complications: not reported
		ITA
		• Insulin independence: 0–50% at 5 yr
		• Change in HbA_{1c} levels: not reported
		• Complications: not reported

(*continued*)

Table 34.2 (*Continued*)

Author, year, country	Patients and methods	Main results

Lehmann et al., 2015, Switzerland [144]	Prospective cohort
	Type 1 diabetes with ESRD
	SPK/PAK: 93/1, total = 94
	• Induction IS: ATG (SPK) or basiliximab (PAK)
	• Maintenance IS: TAC + MMF
	• Mean age (SD): 44.2 (7.6) yr
	• Mean duration of diabetes (SD): 32.1 (8.2) yr
	SIK/IAK: 23/15, total = 38
	• Induction IS: ATG (SIK) or basiliximab (IAK and reinfusions)
	• Maintenance IS: TAC + SRL (later changed to MMF)
	• Mean age (SD): 51.8 (9.0) yr
	• Mean duration of diabetes (SD): 37.0 (11.0) yr
	• Mean total IEQ/kg (SD): 11 408 (10 380)
	  ○ Mean number of infusions (SD): 2.1 (1.3)
		SPK/PAK
		• Insulin independence: 73.6% at 5 yr
		• Mean decrease in HbA_{1c} levels: 7.8% ➔ 5.9% (62 mmol/mol ➔ 41 mmol/mol)
		• Survival at 10 yr: 88.5%
		• Complications:
		  ○ 9/94 (9.6%) graft explants, 39/94 (41.5%) individuals with early laparotomy (45 total laparotomies, only 4 not related to the pancreas transplantation)
		  ○ eGFR decline of 9.5 ± 23.3 ml/min/1.73 m^2 at 13 yr post-transplant
		SIK/IAK
		• Insulin independence: 9.3% at 5 yr
		  ○ 20% mean decrease of insulin dosing (in those without insulin independence)
		• Mean decrease in HbA_{1c} levels: 8.0% ➔ 6.5% (64 mmol/mol ➔ 48 mmol/mol)
		• Drop in severe hypoglycaemia: 346 ± 445 per 100 patient-years to 11.1 ± 15.2
		• Patient survival at 10 yr: 65.4%
		• Complications:
		  ○ 4/38 (10.5%) early laparotomy (only 2 related to the islet transplant)
		  ○ 1 death (accidental puncture of an intercostal artery)
		  ○ eGFR decline of 13.3 ± 13.8 ml/min/1.73 m^2 at 13 yr post-transplant

Moassesfar et al., 2016, USA [151]	Retrospective cohort
	Type 1 diabetes without ESRD
	PTA: 15
	• Induction IS: ATG + MPDN
	• Maintenance IS: MMF + TAC + PDN (tapering)
	• 6 females (40%)
	• Mean age (SD): 42.5 (10.45) yr
	• Mean duration of diabetes (SD): 29.9 (8.1) yr
	ITA: 10
	• Induction IS: ATG + MPDN. 2nd infusion: basiliximab
	• Maintenance IS: belatacept (n = 5) or efalizumab (n = 5) + SRL ± MMF
	• 1 female (10%)
	• Mean age (SD): 51.8 ± 8.3 yr
	• Mean duration of diabetes (SD): 40.3 (11.1) yr
	• Mean total IEQ/kg (SD): 12952 (NR)
	  ○ One infusion: 6 (60%)
	  ○ Two infusions: 4 (40%)
		PTA
		• Mean duration of insulin independence: 55 mo, 93% at 1 yr, 64% at 3 yr
		• Mean decrease in HbA_{1c} levels: 7.3% ➔ 5.5% (56 mmol/mol ➔ 36 mmol/mol)
		• Complications:
		  ○ Surgical: 9/15 (4 requiring pancreatectomy), medical: 3/15, vascular: 1/15, infectious: 3/15 (1 readmission for surgical site infection), renal: 7/15 (1 patient needing dialysis)
		  ○ Change in eGFR: 86.3 ± 18 ml/min/1.73 m^2 ➔ 67.9 ± 25.4 ml/min/1.73 m^2 (p = 0.025 vs baseline)
		• Costs: $134 748
		• Mean duration of hospitalization: 12 d
		ITA
		• Mean duration of insulin independence: 35 mo, 90% at 1 yr, 70% at 3 yr
		• Mean decrease in HbA_{1c} levels: 7.2% ➔ 5.7% (55 mmol/mol ➔ 38 mmol/mol)
		• Complications:
		  ○ Surgical: 0/10, medical: 1/10, vascular: 2/10, infectious: 1/10, renal: 4/10
		  ○ Change in eGFR: 79 ± 13.7 ml/min/1.73 m^2 ➔ 72.9 ± 20.4 ml/min/1.73 m^2 (p = 0.5 vs baseline)
		• Costs: $138 872
		• Mean duration of hospitalization: 5.75

Voglova et al., 2017, Czech Republic [152]	Retrospective cohort
	Type 1 diabetes without ESRD
	PTA/PAK: 36/13, total = 49
	• Induction IS: ATG + MPDN + basiliximab (PAK)
	• Maintenance IS: TAC + MMF + PDN (tapering)
	• Median age (IQR): 39 (33–50) yr
	• Median duration of diabetes (IQR): 24 (16.5–31) yr
	ITA/IAK/SIK: 24/4/2, total = 30
	• Induction IS: ATG + MPDN + etanercept
	• Maintenance IS: TAC + SRL
	• Median age (IQR): 48.5 yr (37–57) yr
	• Median duration of diabetes (IQR): 27.5 (19.5–34) yr
	• Median total IEQ/kg (IQR): 12349 (6387–15 331)
	  ○ One infusion: 11 (36.6%)
	  ○ Two infusions: 9 (27.3%)
	  ○ Three infusions: 10 (33.3%)
		PTA/PAK
		• Insulin independence: 73% at 1 yr, 68% at 2 yr, 55% at 5 yr
		• Mean decrease in HbA_{1c} levels: 7.4% ➔ 4.1% (57 mmol/mol ➔ 21 mmol/mol)
		• Complications:
		  ○ 11 individuals (22.2%) had a graftectomy
		  ○ Surgical revision had to be performed in 23 individuals (47%)
		  ○ eGFR decreased at 2 and 5 yr from 78.6 (63.6–97.8) ml/min/1.73 m^2 to 61.2 (39.6–76.8) and 58.8 (41.4–77.4) ml/min/1.73 m^2, respectively
		ITA/IAK/SIK
		• Insulin independence: 5 individuals (17%) temporal insulin independence
		  ○ 10 patients (42%) with >30% insulin dose reduction
		• Mean decrease in HbA_{1c} levels: 7.4% ➔ 5.8% (57 mmol/mol ➔ 40 mmol/mol)
		• Complications:
		  ○ Bleeding in 10 individuals (33%), 8 (27%) required urgent operation
		  ○ 4 individuals (13%) with an intrahepatic haematoma
		  ○ 1 individual (3.3%) with portal vein thrombosis
		  ○ No significant change in eGFR at 2 and 5 yr follow-up

ATG, antithymocyte globulin; CITR, Collaborative Islet Transplant Registry; CMV, cytomegalovirus; CsA, cyclosporine A; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HbA_{1c}, glycated haemoglobin; IAK, islet-after-kidney transplantation; IEQ, islet equivalent; IL-2, interleukin-2; IQR, interquartile range; IS, immunosuppression; ITA, islet transplantation alone; MMF, mycophenolate mofetil; MPDN, methylprednisolone; PAK, pancreas-after-kidney transplantation; PDN, prednisone; PTA, pancreas transplantation alone; SD, standard deviation; SIK, simultaneous islet–kidney transplantation; SPK, simultaneous pancreas–kidney transplantation; SRL, sirolimus; TAC, tacrolimus.

(i.e. HbA_{1c} levels), on the other hand, seem to be *better* with whole pancreas transplantation compared to islet cell transplantation, although the clinical impact remains unknown.

Finally, there is evidence that a whole pancreas transplant after a failed islet cell transplant has similar benefits to a primary whole pancreas transplant, despite the potential for sensitization [154]. Similarly, a small case series suggests that islet cell transplantation after a failed whole pancreas transplant may be a feasible alternative given the complexity of a second major surgical procedure [155]. Accordingly, whole pancreas and islet cell transplantation should be looked at as complementary rather than competing therapies.

Whole pancreas and islet cell transplantation: challenges and potential solutions

The main challenges for β-cell replacement therapies concern:

- Organ or tissue source and preservation.
- Peri-procedural management, including postoperative care or complications and engraftment.
- Chronic immunosuppression.

These challenges predominate at different moments during the transplantation process (Figure 34.3). While out of the scope of this chapter, several interesting aspects regarding potential solutions to these challenges will be discussed.

Organ or tissue source and preservation

The lack of organs or tissues affects both whole pancreas and islet cell transplantation. Currently, only ~17% of donors have pancreas graft recovery with the intention to transplant [156]. Multidisciplinary strategies including changes in legislation (i.e. *opt-out* policies for organ donation), together with national transplant coordination networks and coordinators (i.e. organ donation specialists in every hospital) and promotion of a culture of donation (physician and public driven), could substantially increase the pool of donors [157]. Other strategies to increase the quality (and quantity) of organs for transplantation involve organ perfusion and preservation technologies. These have evolved over the years; however, while there is pre-clinical evidence of improved outcomes with both whole pancreas [158, 159] and islet cell transplantation [160], research is scarce in comparison to kidney, liver, and lung grafts [161]. These technologies, nevertheless, could expand the donor pool to include marginal donors (e.g. donation after cardiac death), and should be further explored in the future.

Islet isolation for transplantation consumes a significant proportion of the costs [162], which demands resource optimization. Many of these are fixed costs, so central or regional isolation hubs might be a strategy. Another approach is standardization of donor selection. Scores like the North American Islet Donor Score, which have been derived by studying donor characteristics associated with successful isolations (>400 000 IEQ per pancreas), could be useful to optimize donor selection for islet isolation [163]. Optimization of enzymatic digestion [164] and post-isolation islet culture or preservation (~15–20% of the isolated islets are lost during culture) [165] are also actively being investigated. Increasing islet yield and quality to reduce the number of pancreata needed to support long-term glycaemic management after transplantation is a vital research avenue that should continue to be explored in the future.

Perhaps the most exciting developments concerning tissue source for β-cell replacement therapies relate to xenotransplantation and stem cell–based therapies. Islet xenotransplantation has been steadily moving towards the clinic over the past decades. Preliminary clinical experience with xenotransplantation, although limited, has demonstrated safety, albeit with moderate efficacy. This might be explained by the overall lower doses used and the stronger immune responses compared to human islet cell transplantation. However, recent results are promising, showing a 45% decrease in insulin requirements and a 22.5% decrease in HbA_{1c} levels at one year post-transplant of neonatal pig islets [166]. Immune responses following xenotransplantation have also been tackled by using cellular encapsulation (see later), with documented survival of encapsulated neonatal porcine islet for up to 9.5 years [167]. The risk of zoonosis, particularly with the porcine-endogenous retrovirus, has been proven to be mostly theoretical, as no cases of *in vivo* transmission in pre-clinical and clinical trials have been documented [168]. Considering the advances in large-scale isolation of porcine islets, more clinical trials with xenotransplantation in the near future are expected.

Regarding stem-cell therapies in type 1 diabetes, there are two sources for cellular products: human embryonic stem cells (hESCs) and human-induced pluripotent stem cells (hiPSCs). Stem-cell therapies build on recapitulating *in situ* islet differentiation processes (i.e. embryogenesis) to generate functional human islets *in vitro*. Stem-cell therapies provide a potentially unlimited islet supply, but also the capacity to modify cell products to optimize their potency and decrease or even eliminate their immunogenicity [169]. Additionally, hiPSCs offer the possibility of individualized regenerative therapies. Islet-like structures differentiated from hESCs were the first to show similar potency to mature islets in terms of diabetes reversal in mouse models [170–172]. After Takahashi and Yamanaka first generated hiPSCs in 2006 [173], efforts permeated into the field of diabetes and hiPSC-derived islet-like structures were quickly generated from individuals with type 1 diabetes [174]; demonstration of diabetes reversal in mouse models promptly followed [175] and has been increasingly reported in recent years [176]. Whether hESCs or hiPSCs are similar in their capacity to generate functional human islets and in their translational potential is debated. Ethical considerations favour hiPSCs, but aspects regarding genome integrity and regulation, abnormal developmental potential, as well as costs and scalability should also be considered. Currently, hESCs have accumulated more evidence than hiPSCs in terms of differentiation efficiency and overall safety; clinical trials in people with type 1 diabetes are limited to hESC-derived islet-like cells (NCT03162926, NCT03163511, NCT02239354, and NCT02939118). However, the unavoidable fact that hiPSCs represent the only option for truly personalized regenerative medicine is a strong argument driving ongoing research efforts.

Peri-procedural care

There are distinct challenges associated with peri-procedural care in whole pancreas and islet cell transplantation. Optimal donor and recipient selection, as well as pre-transplant care, is essential to decrease the incidence of peri- and post-transplant complications. To optimize donor selection in whole pancreas transplantation, there are identified risk factors and tools, such as the pancreas donor risk index (PDRI) and the pre-procurement pancreas allocation suitability score (P-PASS), which have been used to assess the quality of the graft, the risk of allograft failure, and complications such as graft thrombosis [177]. However, they have not been widely implemented

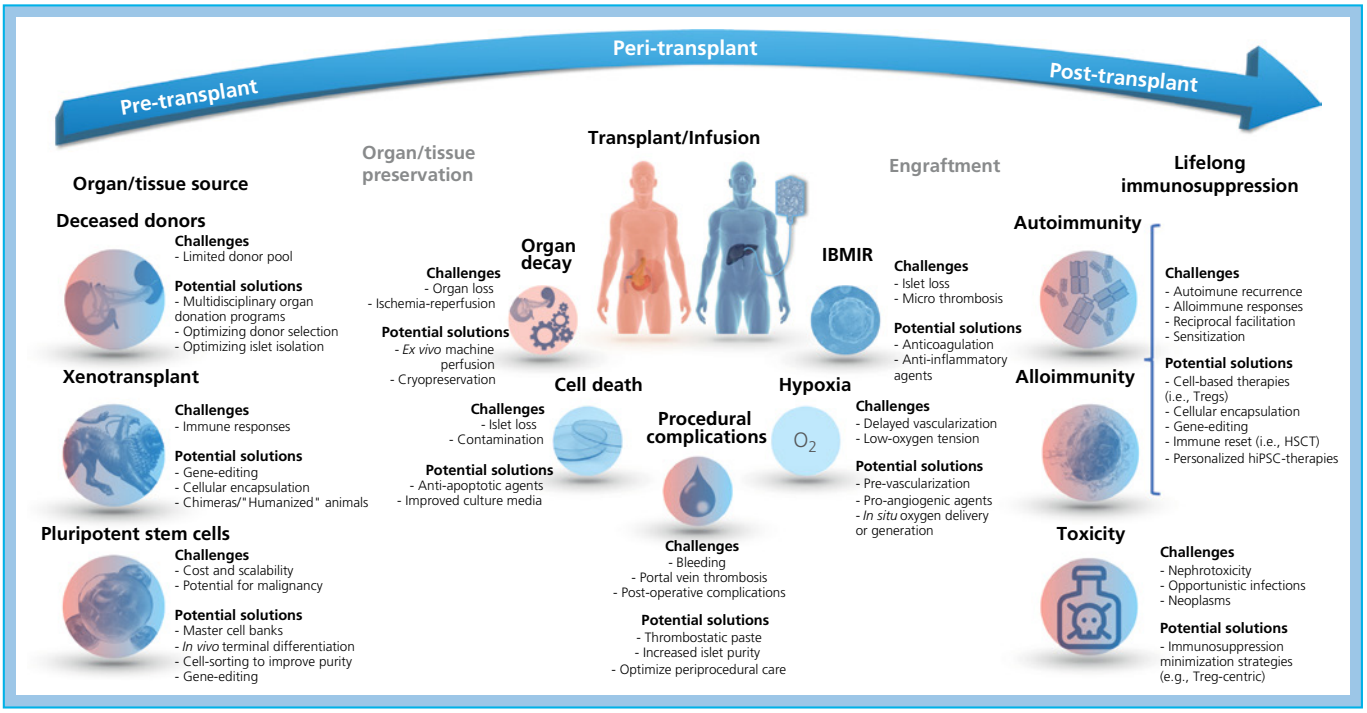

Figure 34.3 Challenges to advance β-cell replacement therapies and potential solutions. The relative importance of these challenges within the context of each type of transplant is highlighted using different colours: red for whole pancreas and blue for islet cell transplantation. hiPSC, human-induced pluripotent stem cell; HSCT, haematopoietic stem cell transplantation; Treg, regulatory T cell.

and, since donors are still relatively scarce, rejecting organs based on any score may not be cost-efficient. Aspects related to surgery, such as optimal back-table preparation, the use of intravenous heparin at the moment of implantation, avoidance of venous extension grafts, as well as avoidance of intraoperative hypotension, should be considered to decrease the risk of major complications after whole pancreas transplantation such as bleeding and thrombosis [178].

Acute graft pancreatitis is another issue. While *physiological* pancreatitis occurs in most cases, this condition has uncertain clinical implications. Mannitol, furosemide, and octreotide have been recommended prior to completion of the vascular anastomosis to prevent this condition [178]. Conversely, early pancreatitis (<3 months post-transplant) occurs in 3–38% of cases, while late acute pancreatitis (>3 months post-transplant) occurs in 14–25% of cases [178]. Risk factors for pancreatitis are related to the donor (i.e. age >50 years, cardiovascular death, haemodynamic instability prior to procurement), graft procurement and preparation, surgery (i.e. bladder exocrine drainage), and infections (i.e. cytomegalovirus). It is important to prevent this outcome, since it decreases graft and patient survival [179].

The only way of decreasing the incidence of postoperative complications is by gaining experience with surgical techniques and peri-procedural care. Unfortunately, the number of whole pancreas transplants has decreased in recent years, which raises concerns for a potential surge in technical complications related to a lack of exposure and inexperience with this procedure [156]. The reasons for this decrease are multifactorial and include a lack of referral of suitable recipients, the competition with novel insulin therapies and islet cell transplantation, as well as the excitement over novel therapies (e.g. immunotherapies, stem cell–based therapies), and the lack of dissemination of improving outcomes, among others [180]. A potential approach is to conduct outreach sessions involving engaged physicians (e.g. transplant surgeons, endocrinologists) and recipients. Expanding the recipient pool (e.g. older, non-type 1 diabetes individuals), which ultimately drives the need for pancreatic grafts, is another alternative [180]. This would increase experience and have positive impacts on the quality of the surgical procedures involved in whole pancreas transplantation.

There are two major complications following islet cell transplantation: bleeding and portal thrombosis. The overall incidence of bleeding after islet cell transplantation is 7%, the main risk factors being high-dose heparin (>45 IU/kg) and the number of infusions [181]. The use of coils or haemostatic agents (e.g. Avitene™, Becton, Dickinson, Franklin Lakes, NJ, USA; or D-Stat™, Teleflex, Wayne, PA, USA) to obliterate the percutaneous tract substantially decreases the risk of major bleeding [182]. This allows safer initiation of systemic anticoagulation with intravenous heparin [31, 59], which ameliorates the instant blood-mediated inflammatory response and contributes to preventing portal vein thrombosis. This latter complication presents in 3–10% of cases, typically as a partial thrombosis. Risk factors include a portal pressure during infusion of >22–25 mmHg, a large packed-cell volume (>5.5 ml or 0.25 ml/kg), and thrombophilic disorders [31], thus these scenarios should be avoided [31, 182].

Early cell death is another major concern in islet cell transplantation, and one of the main explanations behind the need for repeated infusions. The surviving islet mass directly correlates with graft survival [183]. Unfortunately, at least 25% of islets are lost within minutes of infusion into the portal circulation [184]; the central phenomenon believed to explain this is the instant blood-mediated inflammatory response, an innate immune response triggered by direct exposure of islets (and tissue factor) to blood. It compromises activation of the coagulation cascade, the complement pathway, cytokine secretion, and cell-mediated injury [185]. Blocking this response with anticoagulation [59] and anti-inflammatory agents such as TNF-α inhibitors (etanercept) and interleukin-1 inhibitors (anakinra) improves clinical outcomes [60, 121, 151]. Finally, hypoxia represents another relevant factor affecting islet survival. β cells are ill-equipped to handle hypoxia and reactive oxidative stress due to low expression of antioxidants [186]. The process of neovascularization after infusion requires ~7–14 days [187], and many islets die within this period. Strategies to decrease hypoxia and enhance vascularization, even in the most hostile implantation sites (i.e. the subcutaneous space), using pre-vascularization [188], extracellular matrix-based scaffolding, proangiogenic factors, co-culture, or co-transplantation with pro-angiogenic supporting cells, show promise and great potential for clinical translation [189].

Chronic immunosuppression

The need for lifelong immunosuppression is perhaps the greatest obstacle to β-cell replacement therapies becoming a true cure for diabetes. The holy grail of transplantation is operational tolerance; that is, maintaining organ or graft function and survival without immunosuppression. Unfortunately, the probability of achieving operational tolerance after whole pancreas or islet cell transplantation is minimal compared to other organs (e.g. the liver). This may be explained by the underlying autoimmune process in most individuals, which may potentiate alloimmune responses after transplant and vice versa (reciprocal facilitation or regulation) [190].

Despite the hostile immunological milieu, there are potential approaches to minimize or even eliminate the need for lifelong immunosuppression. First, certain immunosuppressants may work better than others at controlling autoreactivity. For example, ATG (compared to daclizumab) and tacrolimus or MMF (compared to sirolimus) have been associated with an increased risk of autoantibody recurrence in people undergoing islet cell transplantation [190]. This has motivated an interest in the *off-target* immunoregulatory effects of pharmacological immunosuppression, such as those involving regulatory T cells (Tregs). In this sense, a *Treg-centric* view on immunosuppression post-transplant has been contemplated [191]. Tregs are central in immunological tolerance and key players in autoimmune diseases. In transplantation, these cells have gained astounding research momentum [192]. Recent studies suggest that different immunosuppressants evoke distinct Treg responses, and that these can potentially be used to foster a Treg-rich environment post-transplant. Alemtuzumab [193] and ATG + daclizumab [194] have both been associated with increased Treg percentages and higher Treg-to-effector T-cell ratios following islet cell transplantation. Sirolimus and MMF have a Treg-favouring effect compared to tacrolimus and cyclosporine A [195]. These preliminary findings should be deepened and extended to other immunosuppressants, as well as to other immunoregulatory mechanisms beyond Tregs.

Other interesting research avenues include adoptive cell transfer (ACT) therapies, cellular encapsulation, and cellular gene editing. Clinical trials using Treg-based ACT therapies have demonstrated safety and efficacy in delaying disease progression in people with type 1 diabetes [196, 197]. In transplantation, the multicentre ONE study showed that Treg-based ACT following kidney transplantation enabled minimization of immunosuppression (i.e. tacrolimus monotherapy) in 40% of individuals compared to 2% of those in the standard care group [198].

Additionally, ACT-treated individuals showed significantly lower rates of opportunistic infections compared to controls [198], which suggests that these therapies provide a more nuanced regulation of immune responses than pharmacological immunosuppression. Enhanced and more targeted cellular products, such as donor alloantigen-reactive Tregs (darTregs) or chimeric T-cell receptor Tregs (CAR-Tregs) [199], are entering the clinical realm, which will further elucidate the potential of ACT therapies to enable operational tolerance.

Cellular encapsulation, which involves providing a physical barrier made of different biomaterials to protect cells from the immune responses, represents a promising alternative to abrogate immunosuppression altogether. Naturally, these technologies apply only to islet cell transplantation and stem cell-based therapies, as it is not possible to encapsulate a whole pancreas. Overall, the clinical and pre-clinical experience is encouraging. The introduction of low-fouling, immune-friendly biomaterials [200] and composite bioscaffolds enabling localized immunosuppression and immunoregulation [201, 202] has resulted in improved graft acceptance and longer duration of diabetes reversal in pre-clinical models of islet cell transplantation. Moreover, these strategies are compatible with xenotransplantation [203] and stem-cell therapies [204–206]. Clinical trials are ongoing with encapsulated hESC-derived pancreatic endocrine progenitors (ViaCyte, San Diego, CA, USA) that differentiate into fully mature islet-like structures *in vivo*, but preliminary results suggest that these cells can survive for up to two years within macroencapsulation devices [207]. Achieving safe and effective cellular encapsulation could broaden indications for β-cell replacement therapies to individuals with other forms of diabetes.

Finally, the advent of efficient gene-editing techniques to prevent allo- [208, 209] and autoimmune [210] destruction of stem cell–derived islets could revolutionize the field. In this regard, ViaCyte has developed the cellular product PEC-QT, an edited clonal hESC line that lacks the β2-microglobulin gene and express a transgene encoding PD-L1 (programmed death-ligand 1) to protect cells from immune attack [211]. It is expected that many of these potentially game-changing strategies will move into clinical trials soon.

Conclusion

β-cell replacement therapies are now consolidated options in the therapeutic arsenal of physicians caring for people with diabetes and persistent problematic hypoglycaemia. The path to clinical success has been paved by brilliant researchers who have carried the field forward with unwavering perseverance and uninterrupted innovation. Today, both whole pancreas and islet cell transplantation are safe and effective. Additionally, both therapies improve life expectancy and have positive impacts on the natural history of diabetes by ameliorating the progression of chronic complications. For these notable achievements, they have earned the well-deserved title of potential cures for diabetes. While it is tempting to compare them to each other, whole pancreas and islet cell transplantation seem to benefit different populations and have their specific niches. In this regard, they can perfectly function as complementary therapies and succeed when the other one has failed.

Currently, β-cell replacement therapies are limited to a very selected group of individuals in which the benefits outweigh the risks associated with these procedures. The main challenges include expanding the supply of organs or tissues to treat as many individuals as needed, optimizing peri-procedural care to decrease procedural risks, and minimizing or eliminating the need for lifelong immunosuppression to avoid long-term adverse effects. Fortunately, the legacy of those brilliant, persistent, and innovative researchers endures and continues to thrive in today's graduate students, scientists, and clinicians involved in the field of β-cell replacement therapies. In the past, the paradigm in diabetes care changed from saving to treating people with diabetes, but the moment has come to shift our paradigm once again from treating to curing people with diabetes.

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35 Oral Glucose-Lowering Agents

Clifford J. Bailey[1] and Andrew J. Krentz[2,3]

[1] School of Life and Health Sciences, Aston University, Birmingham, UK
[2] Institute for Cardiovascular and Metabolic Research, University of Reading, Reading, UK
[3] Department of Population Health Sciences, King's College London, London, UK

Key points

- Treatment of hyperglycaemia is a fundamental part of the management of type 2 diabetes in order to address acute symptoms and to prevent, defer, or reduce the severity of chronic microvascular and macrovascular complications.
- Treating type 2 diabetes is complicated by the multivariable and progressive natural history of the disease. Insulin resistance, a progressive decline in β-cell function, and defects of other gluco-regulatory hormones and of nutrient metabolism give rise to continually changing manifestations of the disease that require therapy to be adjusted accordingly. People with diabetes often have overweight or obesity, exhibit substantial comorbidity and elevated cardiovascular and renal risk, and receive many other medications that may further complicate treatment.
- Care plans and treatment programmes should be tailored to fit the prevailing circumstances of the individual. Lifestyle management (diet and exercise) should be emphasized from the time of diagnosis and reinforced thereafter. Drug treatment should be undertaken promptly if lifestyle intervention does not achieve adequate glycaemic levels.
- Choice of drug therapy should ideally address underlying pathophysiology, but any safe means of restraining the escalating hyperglycaemia may be appropriate. Combinations of differently acting agents are frequently required to provide additive efficacy, and single-tablet, fixed-dose combinations are available to facilitate therapy. Contraindications and precautions associated with each component of pharmacotherapy must be respected.
- The biguanide metformin is often selected as initial oral glucose-lowering therapy. It counters insulin resistance and lowers blood glucose through several insulin-dependent and -independent mechanisms, notably reducing hepatic glucose production, increasing intestinal glucose-lactate turnover, and increasing glucose uptake by skeletal muscle. It does not stimulate insulin secretion, carries a low risk of hypoglycaemia, and does not cause weight gain. Metformin also exerts several potentially beneficial effects on cardiovascular risk factors independently of glycaemic levels, with evidence of improved long-term cardiovascular outcomes. Metformin may be conveniently combined with other classes of anti-diabetes drugs. Gastrointestinal side effects including diarrhoea limit the use of metformin in some people. The rare but serious adverse effect of lactic acidosis precludes use of the drug in people with severe renal insufficiency, advanced liver disease, or any condition predisposing to hypoxia or hypoperfusion, including decompensated heart failure or respiratory failure.
- Sulfonylureas (e.g. gliclazide, glimepiride, glibenclamide/glyburide, glipizide) act on the pancreatic β cells to stimulate insulin secretion. They bind to the transmembranal complex of sulfonylurea receptors SUR1 with ATP-sensitive Kir6.2 potassium efflux channels. This closes the channels, depolarizes the membrane, opens voltage-dependent calcium channels, and raises intracellular free calcium concentrations. This in turn activates proteins that regulate insulin secretion. The efficacy of sulfonylureas depends on adequate residual β-cell function. Hypoglycaemia is the most serious adverse effect, particularly with longer-acting sulfonylureas and in older people. Caution with hepatic and/or renal insufficiency is warranted in accordance with the metabolism and elimination of individual preparations, and interactions with other protein-bound drugs can occur.
- Meglitinides (repaglinide and nateglinide), also known as prandial insulin releasers, are rapid- and short-acting insulin secretagogues taken before meals to boost insulin levels during digestion, thereby reducing prandial hyperglycaemia and decreasing the risk of inter-prandial hypoglycaemia. They act in a similar manner to sulfonylureas by binding to a benzamido site on the SUR1–Kir6.2 complex. They are conveniently used in combination with an agent that reduces insulin resistance.
- Dipeptidyl peptidase 4 (DPP-4) inhibitors (sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin), also termed gliptins, act predominantly as prandial insulin secretagogues by raising the circulating concentrations of endogenous incretin hormones, notably glucagon-like peptide 1 (GLP-1). This enhances the 'incretin' effect of endogenous GLP-1 to potentiate nutrient-stimulated insulin secretion and reduce excess glucagon secretion. DPP-4 inhibitors are weight neutral and, as monotherapy, they carry a low risk of inter-prandial hypoglycaemia. They are often used in combination with metformin or a thiazolidinedione.
- Sodium–glucose cotransporter-2 (SGLT-2) inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin) increase the elimination of excess glucose in the urine (glucosuria) by reducing glucose reabsorption

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from the renal filtrate. They carry a low risk of hypoglycaemia and the glucosuria facilitates weight loss. Their action is independent of insulin, enabling use with other glucose-lowering agents irrespective of the extent of insulin resistance or β-cell dysfunction, but their efficacy requires adequate renal function. The glucosuria can increase the risk of mycotic genital infection, although an associated osmotic diuresis may assist in blood pressure control. SGLT-2 inhibitors reduce the onset and progression of heart failure and exert renal protective effects independently of their glucose-lowering efficacy. Reductions in cardiovascular and all-cause mortality have been reported in cardiovascular outcome trials of some agents in this class.

- An oral formulation of the GLP-1 receptor agonist semaglutide is available in some regions. It mimics the incretin effect to potentiate nutrient-stimulated insulin secretion and suppress excess glucagon secretion with low risk of hypoglycaemia: it also delays gastric emptying and exerts a satiety effect, typically facilitating weight loss. The GLP-1 receptor agonist class has improved outcome measures of atherosclerotic cardiovascular disease and albuminuria in trials in type 2 diabetes.
- Thiazolidinediones (e.g. pioglitazone) produce a slow-onset glucose-lowering effect, attributed mainly to increased insulin sensitivity. They alter the expression of certain insulin-sensitive genes by stimulating the transcription factor peroxisome proliferator-activated receptor γ, increasing adipogenesis, and rebalancing the glucose–fatty acid (Randle) cycle. Thiazolidinediones can be used as monotherapy or in combination with other classes of glucose-lowering agents. They have a low risk of hypoglycaemia but often cause weight gain. The potential for fluid retention and an attendant risk of congestive heart failure should be borne in mind, especially in combination with insulin. Thiazolidinediones are not recommended for individuals at high risk for cardiac decompensation or women with reduced bone density, and members of this class have been discontinued in some countries.
- α-Glucosidase inhibitors (acarbose, miglitol, voglibose) slow the digestion of carbohydrates by competitive inhibition of intestinal α-glucosidase enzymes. This delays glucose absorption and reduces post-prandial glucose excursions without stimulating insulin secretion. These agents must be used in conjunction with meals rich in digestible complex carbohydrate. They do not cause weight gain or hypoglycaemia as monotherapy and can be used alongside any other glucose-lowering agents.
- The dopamine D2 receptor agonist bromocriptine and the bile sequestrant colesevelam have an indication for the treatment of type 2 diabetes in some countries. Their glucose-lowering mechanisms are unclear, but they do not cause weight gain and carry a low risk of hypoglycaemia.
- As type 2 diabetes advances, combinations of glucose-lowering agents with different modes of action are often required. Eventually β-cell function can become too severely compromised to support the continued use of oral agents alone and/or other non-insulin treatments. Insulin therapy should then be initiated, continuing one or more other agents where appropriate.

Treatment of hyperglycaemia is fundamental to the management of type 2 diabetes. It is required to prevent and relieve acute symptoms and complications of hyperglycaemia; prevent, defer, and reduce the severity of microvascular complications; and afford some benefits against macrovascular complications (Table 35.1) [1]. Correction of the hyperglycaemia is an integral part of individualized care that takes account of coexisting diseases and personal circumstances, offers suitable advice on lifestyle and diet, includes other measures to address modifiable cardiovascular risk, selects realistic targets, and facilitates patient education and empowerment. This chapter focuses on the role of oral blood glucose-lowering agents (other anti-diabetes therapies are addressed in Chapters 36 and 37) in the treatment of type 2 diabetes [2–5].

Table 35.1 Aims of appropriate glycaemic management in type 2 diabetes.

Purpose	Complications
Prevent acute symptoms of hyperglycaemia	Dehydration, thirst, polyuria, blurred vision, increased infections
Prevent acute complications	Hyperosmolar non-ketotic state
Prevent, defer, or reduce severity of chronic complications	Microvascular and neuropathic: retinopathy, nephropathy, neuropathy
	Macrovascular: coronary, cerebrovascular, peripheral vascular disease

Pathophysiological considerations

The interdependent multiplicity of genetic and environmental factors underlying type 2 diabetes gives rise to a highly heterogeneous and progressive natural history [1,6,7]. The pathophysiology typically involves defects of insulin secretion *and* insulin action. Obesity, especially visceral adiposity, and abnormalities of glucagon secretion, incretin hormone action, the microbiome, inflammation, and neurotransmitters contribute to the disease process, while cellular disturbances of nutrient metabolism participate as both causes and consequences of glucotoxicity and lipotoxicity [6,7]. An ideal approach to therapy might therefore address the basic endocrine defects, but any other safe means of ameliorating the hyperglycaemia and attendant biochemical disruptions should provide clinical benefits.

The progressive nature of type 2 diabetes was well illustrated by the UK Prospective Diabetes Study (UKPDS), a randomized trial of 5102 individuals with newly diagnosed type 2 diabetes followed for a median of 10 years while receiving either conventional (diet) therapy or intensive therapy with various oral glucose-lowering agents or insulin (Figure 35.1). Note that insulin was introduced earlier than is usual in clinical practice, and insulin was also used as necessary when oral agents were deemed inadequate. Although the glycated haemoglobin (HbA_{1c}) level deteriorated with time irrespective of the treatment, the improvement in glycaemic indices afforded by intensive therapy (median HbA_{1c} reduced by 0.9% [10 mmol/mol]) was associated with a 12% reduction in overall diabetes-related endpoints and a 25% reduction in microvascular endpoints [8]. An epidemiological analysis showed that benefits of intensive therapy continued to accrue until glucose levels were

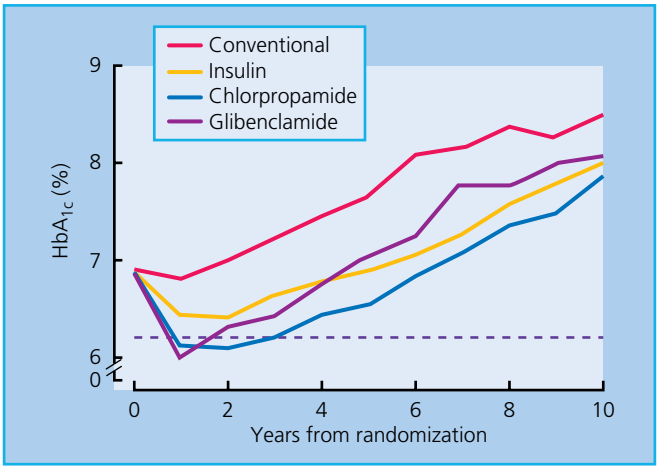

Figure 35.1 The UK Prospective Diabetes Study (UKPDS) shows the progressive rise in glycated haemoglobin (HbA_{1c}) occurring with time in groups receiving conventional (diet) therapy and intensive therapy with various glucose-lowering drugs (two sulfonylureas – chlorpropamide and glibenclamide – and insulin). Source: Data from UK Prospective Study (UKPDS) Group 1998 [8].

returned to the normal range [9]. Moreover, the benefits of earlier intensive management were continued during an unrandomized post-trial follow-up (median 8.5 years) during which glycaemic differences between the former groups were not maintained [10]. This illustrates the glycaemic *legacy effect*, in which early intensive glycaemic management confers an extended reduction in complications, even when glycaemia deteriorates at later stages in the disease process.

Other large randomized trials [11–13] have confirmed fewer microvascular complications among those receiving more intensive glycaemic management (Table 35.2). One such study, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, noted increased mortality during highly intensified (5% mortality, 257/5128) versus standard (4% mortality, 205/5123) glycaemic management. Although the cause of the increased mortality associated with highly intensified management remains uncertain, deaths were more common among those individuals who continued to have hyperglycaemia [14]. In this context, it is noteworthy that an acceptable HbA_{1c} value does not exclude excessive daily fluctuations in blood glucose with hyperglycaemic excursions and hypoglycaemic troughs, the latter often unrecognized nocturnally. Survival following a myocardial event appears to be reduced by both hypo- and hyperglycaemia [15].

Guidelines and algorithms

Factors to consider when selecting a glycaemic target for a particular individual are deliberated in detail in Chapter 37, but it is pertinent to reiterate here that the general principle is to return glycaemia safely as close to normal as practicable, while avoiding hypoglycaemia, minimizing adverse effects on body weight and potential drug interactions, and observing other necessary cautions and contraindications. An individualized approach is recommended. Current treatment algorithms [3,4] provide a framework for initiating and intensifying therapy, but clinical judgement should be applied to harmonize this with the circumstances of the people with diabetes. Thus, a younger, newly diagnosed individual without comorbidity who is responsive to therapy might be expected to meet a more rigorous target, whereas an older, frail individual with comorbidity or a long history of problems with diabetes management may require a less rigorous target. Management of hyperglycaemia should always be part of a comprehensive management programme to address coexisting disease and modifiable cardiovascular risk factors.

It is emphasized that diet, exercise, and other lifestyle measures should be introduced at diagnosis and reinforced at every appropriate opportunity thereafter. These measures can provide valuable blood glucose-lowering efficacy and may initially enable the desired glycaemic target to be achieved. However, even when lifestyle advice is successfully implemented, the progressive natural history of the disease dictates that the majority of people with type 2 diabetes will later require pharmacological therapy, and this should be introduced promptly if the glycaemic target is not met or maintained. Choice of agent is often limited by comorbidities and driven by the need to address obesity, cardiovascular or renal disease, and avoid the risk of hypoglycaemia [3,4]. To date, precision medicine approaches that could provide more personalized pharmacotherapy for people with type 2 diabetes remain underdeveloped. In part, this reflects a deficit of clinically useful biomarkers, for example for insulin action and/or deficiency, together with the limited practical utility of relevant pharmacogenomics. This said, evidence of cardiorenal protective effects of some sodium–glucose cotransporter-2 (SGLT-2) inhibitors and some glucagon-like peptide-1 (GLP-1) receptor agonists has prompted recommendations to refine the treatment algorithm for individuals with type 2 diabetes to consider earlier use of agents with such benefits in individuals at high risk of cardiovascular disease [1,3,4].

The main classes of oral glucose-lowering drugs and their principal modes of action are listed in Table 35.3. Not all agents are available in all countries and prescribing information may vary between countries. The main tissues through which agents exert their glucose-lowering effects are illustrated in Figure 35.2, and the main cautions and contraindications are listed in Table 35.4. Although there are several different classes from which to choose, many dilemmas continue to impinge on both strategy and individualization of treatment. For example, an increase in fasting glycaemia usually accounts for the majority of the total burden of hyperglycaemia in type 2 diabetes; ideally, therefore, this should be adequately addressed using appropriate therapy [16]. It is also pertinent to note the link between post-prandial hyperglycaemic excursions and cardiovascular risk, which mandates the need also to address this component of the hyperglycaemic day profile [17]. Additionally, consideration should be given to the improvements in glycaemic measures that can be achieved through the treatment of obesity [18]. By the time of diagnosis, insulin resistance is usually well established and typically shows only a modest further increase with extended duration of the disease [6,7]. Nevertheless, the association between insulin resistance and cardiovascular risk warrants the amelioration of insulin resistance as a valued therapeutic strategy. The ongoing deterioration in glycaemic measures after diagnosis is considered to be largely attributable to a further progressive decline in β-cell function [6,7]. Thus, preserving β-cell function and mass are important considerations in the quest to maintain long-term glycaemic targets. If β-cell function deteriorates beyond the capacity of oral agents and non-insulin injectable agents (GLP-1 receptor agonists) to provide adequate glycaemic levels, then the introduction of insulin should not be delayed [19]. Incorporating

Table 35.2 Trials comparing intensive with standard (conventional) glycaemic management in type 2 diabetes.

									Relative risk reduction			
									Microvascular		Macrovascular	
Trial	**No.**	**Duration of follow-up (years)**	**Age (years)**	**Duration of diabetes (years)**	**Baseline HbA_{1c} (%)**	**Intensive HbA_{1c}%**		**Conventional HbA_{1c}**	**(%)**	***p***	**%**	***p***
UKPDS	3867[a]	10	53	New	7.1[b]	7.0	vs	7.9	↓ 25	0.009	↓ 16[c]	0.052[d]
UKPDS (post-trial follow-up)	2998	8.5	63	10	—		—		↓ 24	0.001	↓ 15[c]	0.014
ADVANCE	11 140	5	66	8	7.5	6.5	vs	7.3	↓ 14	0.01	↓ 6	0.32[b]
ACCORD[e]	10 251	3.5[e]	62	10	8.3	6.4[e]	vs	7.5	↓ 33	0.005[f]	↓ 10	0.16[b]
VADT	1791	5.6	60	11.5	9.4	6.9	vs	8.4	↓ 2.5[g]	0.05	↓ 12	0.14[b]

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation; DCCT, Diabetes Control and Complications Trial; IFCC, International Federation of Clinical Chemistry; UKPDS, UK Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial. HbA_{1c}, glycated haemoglobin.
↓, decrease.
To convert HbA_{1c} % to IFCC mmol/mol, the following formula should be used: IFCC mmol/mol = 10.93 DCCT% −23.5 mmol/mol.
[a] Participants without obesity.
[b] After a 3 mo dietary run-in.
[c] Myocardial infarction.
[d] Non-significant.
[e] Intensive therapy discontinued at median 3.5 years because of increased deaths in the intensive (257/5128; 5%) vs conventional (203/5123; 4%) group.
[f] Reduction in new or worsening nephropathy. No effect on incidence of progression of retinopathy.
[g] Any increase in albuminuria.

Table 35.3 Classes of oral glucose-lowering drugs and their main modes of action.

Class with examples	Main mode of glucose-lowering action	Main cellular mechanism of action
Biguanide Metformin	Counter insulin resistance (especially decrease hepatic glucose output)	Enhance various insulin-dependent and -independent actions including effects on AMPK, mitochondrial respiratory chain, and insulin receptor signalling
Sulfonylureas Glimepiride, gliclazide, glipizide, glyburide (=glibenclamide)[a]	Stimulate insulin secretion (typically 6–24 h)	Bind to SUR1 sulfonylurea receptors on pancreatic β cells, which closes ATP-sensitive Kir6.2 potassium channels
Meglitinides Repaglinide, nateglinide	Stimulate insulin secretion (faster onset and shorter duration of action than sulfonylureas)	Bind to benzamido site on SUR1 receptors on pancreatic β cells, which closes ATP-sensitive Kir6.2 potassium channels
DPP-4 inhibitors (gliptins) Sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin	Increase prandial insulin secretion	Inhibit DPP-4 enzyme, resulting in increased plasma half-life of incretin hormones, notably GLP-1
Thiazolidinediones (PPAR-γ agonists) Pioglitazone, rosiglitazone[b]	Increase insulin sensitivity (especially increase peripheral glucose utilization)	Activate nuclear receptor PPAR-γ mainly in adipose tissue, which affects insulin action and glucose–fatty acid cycle
Sodium-glucose cotransporter-2 (SGLT-2) inhibitors Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Increase elimination of glucose in the urine	Inhibit SGLT-2 transporters in renal proximal tubules
α-Glucosidase inhibitors Acarbose, miglitol, voglibose	Slow rate of carbohydrate digestion	Competitive inhibition of intestinal α-glucosidase enzymes
Dopamine agonist Bromocriptine[b]	Reduce hepatic glucose production	Central dopaminergic effect
Bile acid sequestrant Colesevelam[b]	Not established	Not established
Glucagon-like peptide-1 (GLP-1) receptor agonist Semaglutide	Increase prandial insulin secretion and reduce glucagon secretion, delay gastric emptying, and exert central effects on increased satiety	Activate GLP-1 receptors on pancreatic β and α cells and in other tissues including upper gastrointestinal tract, portal system, and brain

AMPK, adenosine 5′-monophosphate-activated protein kinase; ATP, adenosine triphosphate; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; PPAR-γ, peroxisome proliferator-activated receptor γ; SGLT-2, sodium–glucose cotransporter-2.
[a] Glyburide is the same active compound as glibenclamide.
[b] Rosiglitazone has been withdrawn in many countries, pioglitazone is no longer available in some countries, and bromocriptine and colesevelam are not widely used for the treatment of type 2 diabetes.

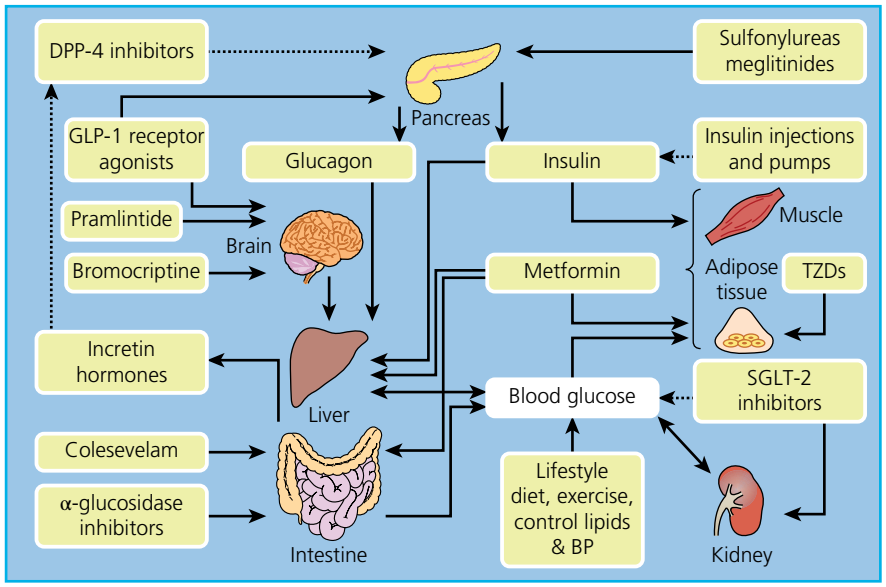

Figure 35.2 Main tissues through which oral glucose-lowering agents exert their glucose-lowering effects. BP, blood pressure; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium–glucose cotransporter-2; TZD, thiazolidinedione.

Table 35.4 General features of the more widely used oral blood glucose-lowering treatments for type 2 diabetes including the main cautions and contraindications.

Feature	Metformin	Sulfonylureas	Meglitinides	Thiazolidinediones	SGLT-2 inhibitors	DPP-4 inhibitors	α-Glucosidase inhibitors	GLP-1 receptor agonist
HbA_{1c} (%)	↓ 1–2	↓ 1–2	↓ 0.5–1.5[f]	↓ 0.5–1.5	↓ 0.5–1.5	↓ 0.5–1.5	↓ 0.5–1	↓ 1–1.5
HbA_{1c} (mmol/mol)	↓ 11–22	↓ 11–22	↓ 6–17[f]	↓ 6–17	↓ 6–17	↓ 6–17	↓ 6–11	↓ 11–17
Body weight	–/↓	↑	↑/–	↑	↓	—	—	↓
Lipids	–/+	—	—	+/–/×	–/+	—	–/+	–/+
Blood pressure	—	—	—	↓/–	↓	—	—	↓
Tolerability	GI[a]	Hypo[d]	Hypo[g]	Fluid retention	Mycotic infection	—	GI[a]	GI[a]
Safety	Lactic acidosis[b]	Hypo[d]	Hypo[g]	Oedema[h] Anaemia Heart failure[i] Fractures	Dehydration[j]	Pancreatitis[l]	—	Pancreatitis[l]
Cautions	Renal Liver Hypoxaemia[c]	Liver Renal[e]	Liver Renal[e]	CV[i]	Renal[k]	Liver[m]	GI[a]	GI[a]

[a] Gastrointestinal side effects.
[b] Lactic acidosis is rare.
[c] Check for adequate renal and hepatic function, avoid in conditions with heightened risk of hypoxaemia.
[d] Risk of hypoglycaemia, occasionally severe.
[e] Check liver and/or renal function relevant to mode of metabolism/elimination.
[f] Mostly act to lower post-prandial hyperglycaemia; lesser impact on fasting glycaemia and on HbA_{1c}.
[g] Lesser risk of severe hypoglycaemia than sulfonylurea.
[h] Fluid retention, anaemia, increased risk of heart failure in susceptible individuals.
[i] Check for pre-existing cardiovascular disease or developing signs of heart disease; controversy regarding possible early increase in myocardial infarction with rosiglitazone not confirmed in long-term prospective studies.
[j] Rare reports of ketoacidosis.
[k] Ensure adequate renal function.
[l] Possible risk of acute pancreatitis.
[m] Monitoring of liver function with vildagliptin.
↑, Increased; ↓, decreased; –, neutral; +, benefit; ×, impair. CV, cardiovascular; DPP-4, dipeptidyl peptidase 4; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; HbA_{1c}, glycated haemoglobin (1% ≈ 11 mmol/mol); Hypo, hypoglycaemia; SGLT-2, sodium–glucose cotransporter-2.

Table 35.5 Drug interactions with oral glucose-lowering agents that may affect their glucose-lowering effects.

Agent	Increase glucose-lowering effect	Decrease glucose-lowering effect
Any	Combination with other glucose-lowering drugs Minor insulin releasers (e.g. aspirin) Minor insulin sensitivity enhancers (e.g. ACE inhibitors, magnesium or chromium supplements)	Agents that impair insulin action (e.g. glucocorticoids, some antipsychotics, minor effects of diuretics, β-blockers, some β_2-agonists) Impair insulin secretion (e.g. octreotide, some calcium channel blockers)
Metformin	Renal cation secretion competition by cimetidine Minor PK interaction with furosemide and nifedipine	—
Sulfonylureas	Reduce hepatic metabolism (e.g. some antifungals and MAOIs) Displace plasma protein binding (e.g. coumarins, NSAIDs, sulfonamides) Decrease excretion (e.g. probenecid)	K^+-ATP channel openers (e.g. diazoxide) Metabolism secondary to enzyme induction (e.g. rifampicin)
Meglitinides	Reduce hepatic metabolism (e.g. gemfibrozil) Potentially displace plasma protein binding	Metabolism secondary to enzyme induction (e.g. rifampicin, barbiturates, carbamazepine)
Thiazolidinediones	Reduce hepatic metabolism, gemfibrozil Potentially displace plasma protein binding	Metabolism secondary to enzyme induction (e.g. rifampicin)
SGLT-2 inhibitors	—	Impaired renal function
DPP-4 inhibitors	Potential interactions with liver and renal metabolism and plasma protein binding	–
GLP-1 receptor agonist	—	If *not* taken on an empty stomach
α-Glucosidase inhibitors	Slow gut motility (e.g. cholestyramine)	Potentially with agents that increase gut motility

ACE, angiotensin-converting enzyme; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; MAOI, monooxidase inhibitor; NSAID, non-steroidal anti-inflammatory drug; PK, pharmacokinetic; SGLT-2, sodium–glucose cotransporter-2.

some or all of these into the treatment process is inevitably a challenge, and the need to explore suitable combinations of therapies to accommodate the changing status of the disease is common practice [3,4].

The increasing prevalence of type 2 diabetes among children, adolescents, and young adults adds an extra long-term dimension to risk–benefit considerations [20]. Although initial adequate intervention remains paramount, there is limited experience with oral glucose-lowering agents in children and adolescents; metformin has been used safely in paediatric practice from 10 years of age; and sulfonylureas have been used in paediatric presentations of certain monogenic forms of diabetes, such as maturity-onset diabetes of the young (MODY). Treating type 2 diabetes in women who are of childbearing age carries the risk of unplanned pregnancy while receiving oral glucose-lowering agents. Treatment with metformin or a sulfonylurea at the time of conception and during the first trimester has not been shown to have any adverse effects on mother or fetus, and judicious use of metformin may reduce miscarriage and gestational diabetes. Insulin remains the preferred glucose-lowering medication in pregnancy, as there is a substantial evidence base for the safety and flexibility of insulin in gestational diabetes. A paucity of evidence, allied with animal toxicity data or theoretical considerations for some classes, contraindicates thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists during pregnancy and lactation.

Older people are more vulnerable to most of the cautions and contraindications for glucose-lowering drugs, and a deterioration in pathophysiological status can occur rapidly, necessitating more frequent monitoring [21]. Hypoglycaemia is a particular concern in this age group. Although safety must be judged on an individual drug–patient basis, it is noteworthy that several commonly used concomitant medications can impair glucose levels (e.g. glucocorticoids, certain antipsychotics, diuretics, and β-blockers), whereas others may have their own minor glucose-lowering effect (e.g. aspirin, some angiotensin-converting enzyme [ACE] inhibitors, and mineral supplements; Chapter 21). The most frequent interactions with glucose-lowering drugs are summarized in Table 35.5.

Descriptive terminology applied to glucose-lowering drugs may simplify the use of the different agents. Hypoglycaemic agents have the capacity to lower blood glucose below normal to the extent of frank hypoglycaemia (e.g. sulfonylureas, meglinitides, and insulin). Anti-hyperglycaemic agents can reduce hyperglycaemia, but when acting alone they do not usually have the capability to lower blood glucose below normoglycaemia to the extent of frank hypoglycaemia (e.g. metformin, DPP-4 inhibitors, thiazolidinediones, SGLT-2 inhibitors, GLP-1 receptor agonists, α-glucosidase inhibitors, bromocriptine, and colesevelam).

Biguanides

Metformin (dimethylbiguanide) is the only biguanide currently used in most countries (Figure 35.3). The history of biguanides stems from a guanidine-rich herb, *Galega officinalis* (goat's rue or French lilac), which was used as a traditional treatment in Europe [22]. Guanidine has a glucose-lowering effect, and several guanidine derivatives were adopted for the treatment of diabetes in the 1920s. These agents all but disappeared as insulin became available, but three biguanides – metformin, phenformin, and buformin – were introduced in the late 1950s. Phenformin and buformin were withdrawn in many countries in the late 1970s because of a high incidence of lactic acidosis. Metformin remained and was introduced into the United States in 1995 [23], and it has since become the most prescribed glucose-lowering agent worldwide [24].

Mode of action

Metformin exerts a range of actions that counter insulin resistance and lower blood glucose; the drug also offers some protection against vascular complications independently of its anti-hyperglycaemic effect (Table 35.6) [25,26]. At the cellular level, metformin exerts insulin-dependent and -independent effects on glucose metabolism that vary with the concentration of metformin to which the tissue is exposed and the prevailing gluco-regulatory mechanisms in that tissue (Figure 35.4). For example, high concentrations of metformin in the intestinal wall can suppress the mitochondrial respiratory chain at complex 1 independently of insulin and promote anaerobic glycolysis to lactate. The conversion of lactate to glucose in other tissues (increased glucose turnover as part of the Cori cycle) may help to prevent weight gain. Lower concentrations of metformin can suppress mitochondrial glycerol-phosphate dehydrogenase and modestly improve insulin sensitivity in liver and muscle, in part by enhancing post-receptor signalling pathways for insulin, and also by effects on nutrient metabolism and energy

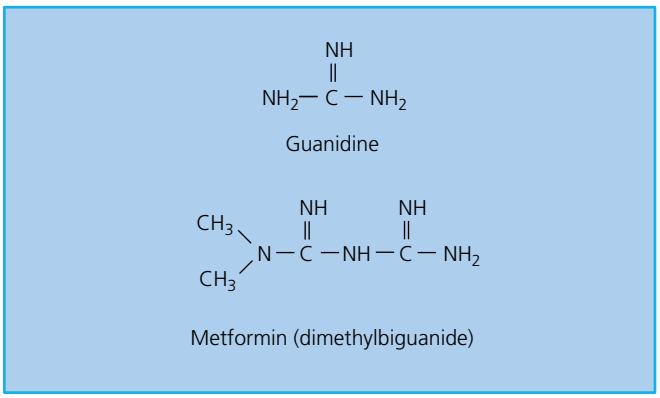

Figure 35.3 Chemical structures of guanidine and metformin.

Table 35.6 Diverse metabolic and vascular effects of metformin.

Features associated with diabetes		Effects of metformin
Hyperglycaemia	↓	↓ HGP, ↑ peripheral glucose uptake, ↑ glucose turnover
Insulin resistance	↓	↑ Receptor-postreceptor insulin signals
Hyperinsulinemia	↓	↓ Fasting and often post-prandial insulin
Obesity	↓/–	↓ Or stabilizes body weight
IGT	↓	↓ Progression to type 2 diabetes
Dyslipidaemia	↓/–	Modest benefits if abnormal ↓ VLDL-TG, ↓ LDL, ↑ HDL May decrease FA oxidation
Blood pressure	–	No significant effect
Pro-coagulant state	↓	Antithrombotic (↓ fibrinogen, ↓PAI-1, ↓ platelet aggregation)
Endothelial function	↑	↓ Vascular adhesion molecules
Atherosclerosis	↓	↓ MI, ↓ stroke, ↑ vascular reactivity, ↓ cIMT, ↑ life expectancy, anti-atherogenic in animals

↑, Increase; ↓, decrease; –, no significant effect.
cIMT, carotid intima-media thickness; FA, fatty acid; HDL, high-density lipoprotein cholesterol; HGP, hepatic glucose production; IGT, impaired glucose tolerance; LDL, low-density lipoprotein cholesterol; MI, myocardial infarction; PAI-1, plasminogen-activator inhibitor-1; VLDL-TG, very low-density lipoprotein cholesterol triglyceride.

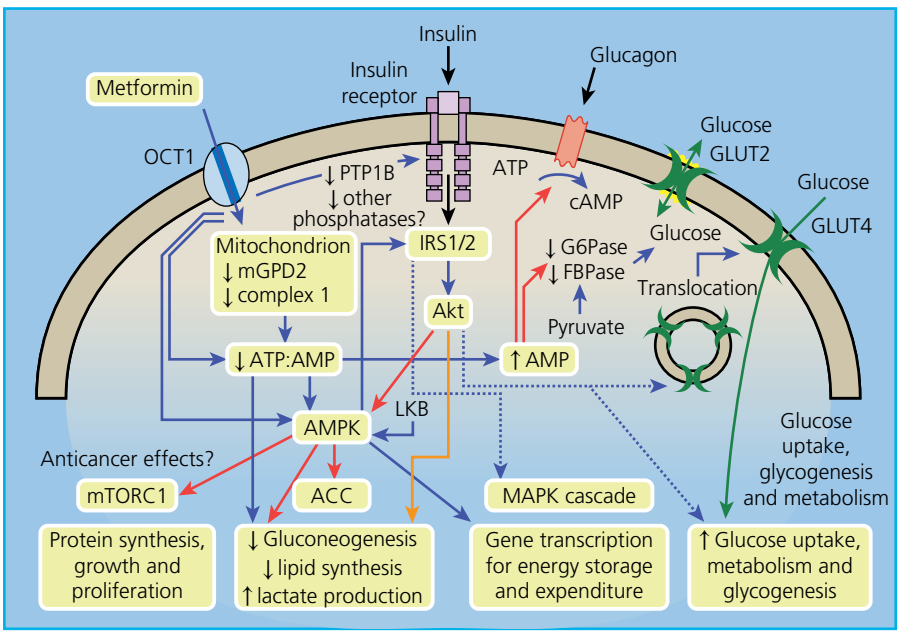

Figure 35.4 Multiple cellular actions of metformin involve insulin-dependent and -independent effects and vary according to the tissue and the level of exposure to metformin. For example, very high exposure to metformin in the intestine can reduce oxidative phosphorylation and promote anaerobic metabolism. Lower concentrations of metformin can improve insulin sensitivity in liver and muscle via effects on insulin receptor signalling and post-receptor signalling pathways of insulin action. Metformin can influence cellular nutrient metabolism and energy production independently of insulin via activation of adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK). ACC, acetyl-CoA carboxylase; Akt, protein kinase B (PKB); AMPK, adenosine monophosphate-activated protein kinase; FBPase, fructose 1,6-bisphosphatase; G6Pase, glucose 6-phosphatase; GLUT, glucose transporter isoform; IRS, insulin receptor substrate; LKB1, liver kinase B1; MAPK, mitogen-activated protein kinase; mGPD, mitochondrial glycerol-phosphate dehydrogenase; mTORC1, mammalian target of rapamycin complex 1; OCT1, organic cation transporter 1; PTP, protein tyrosine phosphatase. Blue lines indicate positive effects; red lines indicate negative effects; dashed lines indicate multistep pathways; up arrows indicate positive effect; down arrows indicate negative effect.
Source: Adapted from Bailey 2012 [27].

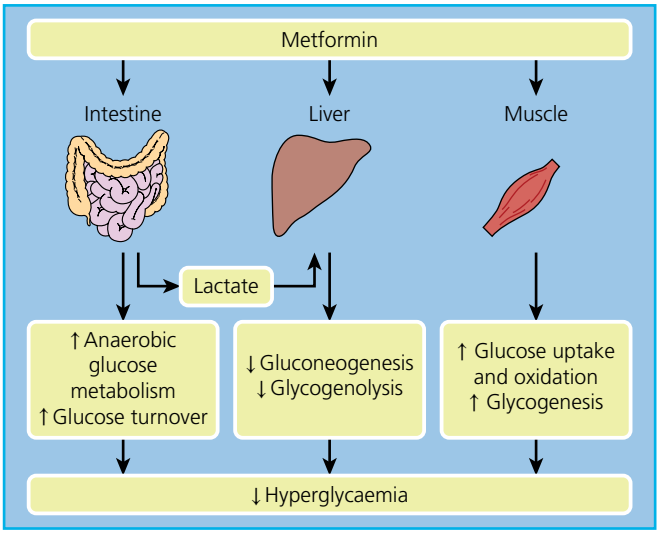

Figure 35.5 Main sites of action of metformin contributing to glucose-lowering effect.

production independently of insulin via activation of adenosine 5'-monophosphate-activated protein kinase (AMPK) [28].

The glucose-lowering efficacy of metformin requires the presence of at least some insulin, because metformin does not mimic or activate the genomic effects of insulin. Also, metformin does not stimulate insulin release; its main glucose-lowering effect appears to be a reduction of hepatic glucose production by suppressing gluconeogenesis and glycogenolysis, but not sufficiently to cause frank hypoglycaemia when used as monotherapy. Metformin reduces gluconeogenesis by increasing hepatic insulin sensitivity, reducing hepatic glucagon receptor signalling, and decreasing hepatic extraction of some gluconeogenic substrates such as lactate (Figure 35.5). Metformin can enhance insulin-stimulated glucose uptake in skeletal muscle by increasing the translocation of insulin-sensitive glucose transporters (GLUT4) into the cell membrane and increasing the activity of glycogen synthase, which promotes glycogen synthesis.

Pharmacokinetics

Metformin is rapidly but incompletely absorbed, shows little binding to plasma proteins, and is not metabolized, and so it does not interfere with co-administered drugs. Metformin is widely distributed at concentrations similar to plasma (about 10^{-5} mol/l), but much higher concentrations are retained in the walls of the gastrointestinal tract. The plasma half-life ($t_{1/2}$) is about 6 hours with elimination of unchanged drug in the urine, mostly within 12 hours [29]. Although renal clearance is achieved more by tubular secretion than glomerular filtration, metformin is contraindicated for people with significant impairment of glomerular filtration. Cimetidine is the only drug known to compete for clearance sufficiently to cause a clinically significant increase in plasma metformin concentrations.

Indications and contraindications

Because metformin does not cause weight gain, it is often preferred for people who have overweight or obesity and type 2 diabetes, although it shows similar anti-hyperglycaemic efficacy in individuals with normal weight [30]. To preclude drug accumulation, patient suitability and dose should be considered very carefully if there is evidence of impaired renal function (e.g. creatinine clearance is <60 ml/min). Starting metformin is not encouraged if the estimated glomerular filtration rate (eGFR) is <45 ml/min/1.73 m^2, although reduced doses of the drug are permitted in most countries down to an eGFR of 30 ml/min/1.73 m^2. Further contraindications include significant cardiac or respiratory insufficiency, or any other condition predisposing to hypoxia or reduced tissue perfusion (e.g. hypotension, septicaemia), and also significant liver disease, alcohol abuse, or a history of metabolic acidosis. Because the potential for acute deterioration in renal, cardiopulmonary, and hepatic function should be considered, it is difficult to identify precise cut-offs for starting or stopping metformin therapy. With this in mind, metformin can be used in older people provided that renal insufficiency and other exclusions are not present. Ovulation can resume in women with anovulatory polycystic ovary syndrome (PCOS), which is an unlicensed purpose for which the drug has been used in the absence of diabetes [31]. Metformin is also under investigation for a possible inhibitory effect on tumour formation and progression in some tissues.

A standard (so-called immediate release, IR) tablet or liquid formulation of metformin should be taken with meals or immediately before meals to minimize possible gastrointestinal side effects. Treatment should start with 500 or 850 mg once daily, or 500 mg twice daily (divided between the morning and evening meals). The dosage is increased slowly – one tablet at a time – at intervals of about 1–2 weeks until the target level of blood glucose is attained. If the target is not attained and an additional dose produces no further improvement, the previous dose should be resumed. In the case of monotherapy, combination therapy can be considered by adding a differently acting agent (e.g. an insulin-releasing drug, SGLT-2 inhibitor, or thiazolidinedione). The maximal effective dosage of metformin is about 2000 mg/day, taken in divided doses with meals, and the maximum is 2550 or 3000 mg/day in different countries [30].

Slow-release formulations (XR/SR/ER) of metformin are available in most countries; they can be taken once daily in the morning, or if necessary morning and evening. Metformin can also be used in combination with any other class of glucose-lowering agent, including insulin, and an extensive range of fixed-dose combination tablets is available in which metformin is combined with either a sulfonylurea, SGLT-2 inhibitor, DPP-4 inhibitor, or thiazolidinedione (see later). It should be noted that although metformin alone is unlikely to cause serious hypoglycaemia, it can occur when metformin is used in combination with an insulin-releasing agent or insulin.

During long-term use of metformin, it is advisable to check at least annually for the emergence of contraindications, particularly renal. Metformin can reduce gastrointestinal absorption of vitamin B_{12}, and although this is rarely a cause of frank anaemia, an annual haemoglobin measurement is recommended, especially for individuals with known or suspected nutritional deficiencies. Metformin should be stopped temporarily when using intravenous radiographic contrast media, or during surgery with general anaesthesia or other intercurrent situations in which the exclusion criteria could be invoked. Substitution with insulin may be appropriate at such times [30].

Efficacy

As monotherapy in people whose diabetes is not adequately managed by lifestyle modification, optimally titrated metformin typically reduces fasting plasma glucose by 2–4 mmol/l, corresponding

to a decrease in HbA_{1c} by ~1–2% (11–22 mmol/mol) [23, 24, 29, 30]. This is largely independent of body weight, age, and duration of diabetes, provided that some β-cell function is still present. To accommodate the progressive nature of type 2 diabetes, it is likely that uptitration of dosage and addition of a second agent will be required to maintain glycaemic targets in the long term.

Metformin carries minimal risk of significant hypoglycaemia or weight gain when used as monotherapy. It may lead to a decrease in basal insulin concentrations, notably in people with hyperinsulinaemia, which should help to improve insulin sensitivity. Minor improvements in the blood lipid profile have been observed during metformin therapy, mostly in those with hyperlipidaemia: plasma concentrations of triglycerides, fatty acids, and low-density lipoprotein (LDL) cholesterol tend to fall, whereas that of high-density lipoprotein (HDL) cholesterol tends to rise [24, 30]. These effects appear to be independent of the anti-hyperglycaemic effect, although a lowering of triglyceride and free fatty acids is likely to help improve insulin sensitivity and benefit the glucose–fatty acid (Randle) cycle.

In the UKPDS, individuals with overweight who started oral glucose-lowering therapy with metformin showed a 39% reduced risk of myocardial infarction (MI) compared with conventional treatment ($p = 0.01$) [32]. There was no obvious relationship with metformin dosage, suggesting that people who can tolerate only a low dose of metformin may benefit from continuing the drug, even when other agents are required to meet adequate glycaemic targets. The decrease in MI was not related to the extent of the glucose-lowering effect of metformin, or effects on classic cardiovascular risk factors such as blood pressure or plasma lipids. Reported benefits of metformin on various atherothrombotic risk markers and factors have been reported, including reduced carotid intima-media thickness (cIMT), increased fibrinolysis, and reduced concentrations of the anti-thrombolytic factor plasminogen activator inhibitor-1 (PAI-1) (Table 35.6) [24, 25, 30].

When metformin is added to the regimens of people receiving insulin therapy, a reduction of insulin dosage is often required, consistent with the ability of metformin to improve insulin sensitivity. Similarly, addition of insulin in people already receiving metformin usually requires lower dosages of insulin and results in less weight gain. Lower amounts of insulin are also associated with fewer and less severe episodes of hypoglycaemia [24, 30]. In some regions of the world metformin is indicated for the prevention of diabetes: the US Diabetes Prevention Program found metformin to reduce the incidence of new cases of diabetes in participants who had overweight or obesity with impaired glucose tolerance (IGT) by 33%, compared with a reduced risk of 58% using an intensive regimen of diet and exercise [33, 34]. The preventive effect of metformin was most evident among individuals who were younger or with a higher level of obesity.

Adverse effects

The main tolerability issue with metformin is abdominal discomfort and other gastrointestinal adverse effects, including diarrhoea. These are often transient and can be ameliorated by taking the drug with meals and titrating the dose slowly. Symptoms may remit if the dose is reduced, but around 10% of people cannot tolerate the drug at any dose. The most serious adverse event associated with metformin is lactic acidosis; it is rare (probably about 0.03–0.06 cases per 1000 patient-years), but about half of cases are fatal [35]. Because the background incidence of lactic acidosis among people with type 2 diabetes has not been established, it is possible that some cases previously attributed to metformin were caused by other factors.

Most reported cases of lactic acidosis in people receiving metformin have been caused by inappropriate prescription, particularly overlooking renal insufficiency. The resulting accumulation of metformin is likely to increase lactate production, and increasing lactate will be aggravated by any hypoxic condition or impaired liver function. Hyperlactataemia occurs in cardiogenic shock and other illnesses that decrease tissue perfusion, and so metformin may be only an incidental factor in some cases. Nevertheless, metformin should be stopped immediately in all cases of suspected or proven lactic acidosis, regardless of cause.

Lactic acidosis is typically characterized by a raised blood lactate concentration (e.g. >5 mmol/l), decreased arterial pH, and/or bicarbonate concentration with an increased anion gap ($[Na^+] - [Cl^- + HCO_3^-] > 15$ mmol/l). Presenting symptoms are generally non-specific, but often include hyperventilation, malaise, and abdominal discomfort. Treatment should be commenced promptly without waiting to determine whether metformin is a cause; bicarbonate remains the usual therapy, but evidence of its efficacy is limited. Haemodialysis to remove excess metformin can be helpful, and may assist restoration of fluid and electrolyte balance during treatment with high-dose intravenous bicarbonate.

Sulfonylureas

Since their introduction in the 1950s, sulfonylureas have been used extensively as insulin secretagogues for the treatment of type 2 diabetes. Sulfonylureas were developed as structural variants of sulfonamides after the latter were reported to cause hypoglycaemia [36]. Early sulfonylureas such as carbutamide, tolbutamide, acetohexamide, tolazamide, and chlorpropamide are often referred to as *first-generation* compounds. These have been largely superseded by more potent *second-generation* sulfonylureas, notably glibenclamide (=glyburide), gliclazide, glipizide, and glimepiride (Figure 35.6).

Mode of action

Sulfonylureas act directly on the β cells of the islets of Langerhans to stimulate insulin secretion (Figure 35.7). They enter the β cell and bind to the cytosolic surface of the sulfonylurea receptor 1 (SUR1), which forms part of the transmembrane complex of ATP-sensitive Kir6.2 potassium channels (K^+ATP channels) (Figure 35.8) [37]. Binding of a sulfonylurea closes the K^+ATP channel, reducing the efflux of potassium and enabling membrane depolarization. Localized membrane depolarization opens adjacent voltage-dependent L-type calcium channels, increasing calcium influx and raising the cytosolic free calcium concentration. This activates calcium-dependent signalling proteins that control the contractility of microtubules and microfilaments that mediate the exocytotic release of insulin granules. Preformed insulin granules adjacent to the plasma membrane are promptly released (*first-phase* insulin release), followed by a protracted (*second-phase*) period of insulin release that begins about 10 minutes later [38]. The second phase of insulin release involves translocation of preformed and newly formed insulin granules to the plasma membrane for secretion. Sulfonylureas continue to stimulate insulin release while they are bound to the SUR1 provided that the β cells are functionally competent. Some desensitization, however, occurs during repeated and protracted stimulation [39]. Because sulfonylureas can stimulate insulin release when glucose concentrations are below the normal

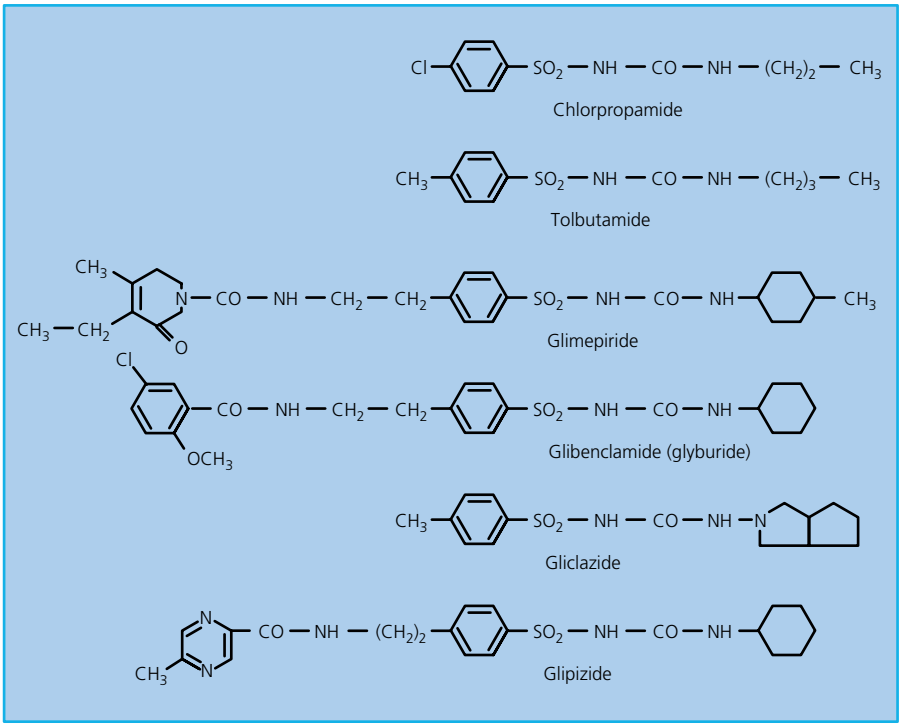

Figure 35.6 Chemical structures of sulfonylureas.

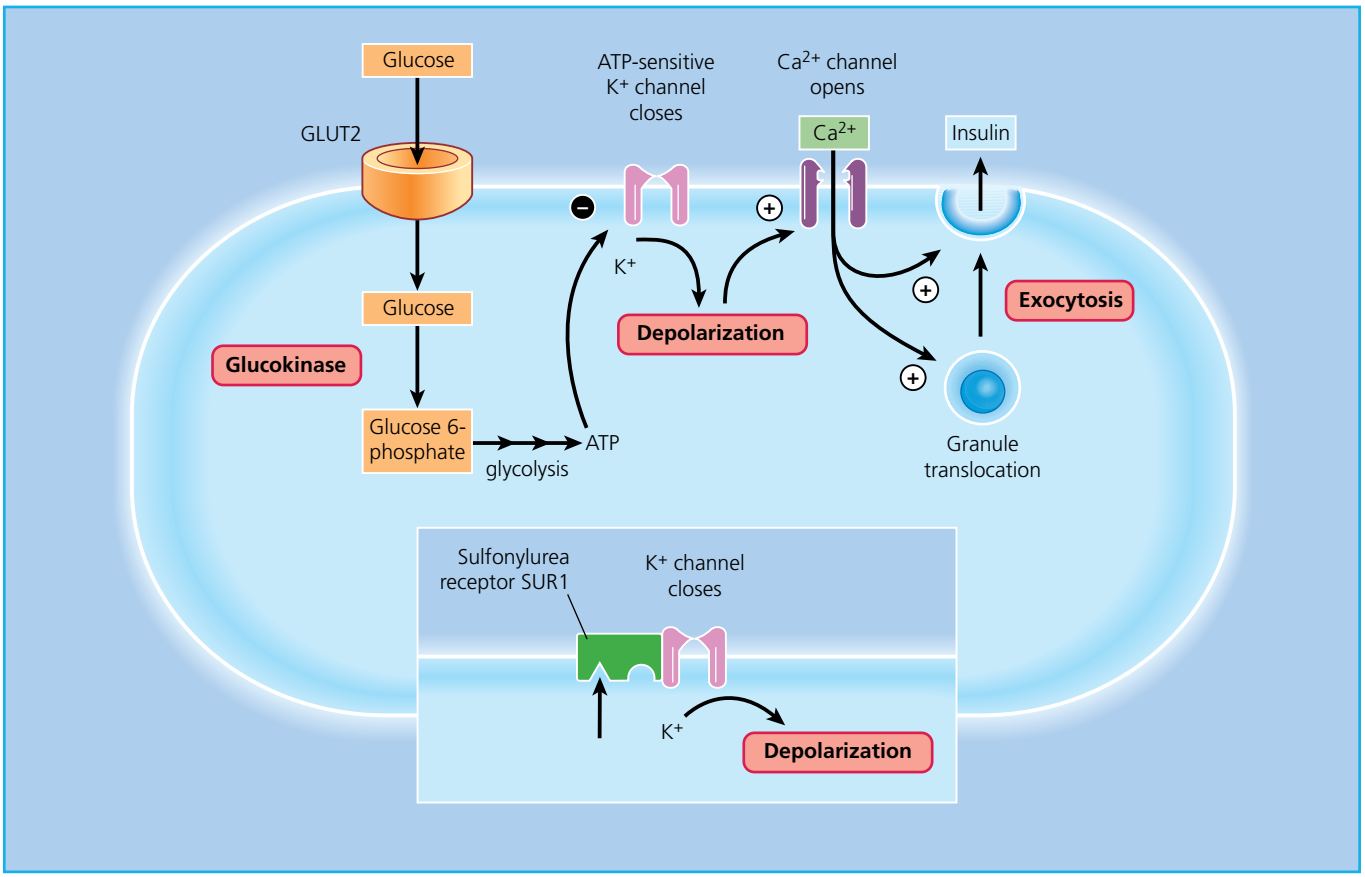

Figure 35.7 Sulfonylureas act on the pancreatic β cell to stimulate insulin secretion. They bind to the cytosolic surface of the sulfonylurea receptor 1 (SUR1), causing closure of ATP-sensitive Kir6.2 potassium channels, depolarizing the plasma membrane, opening calcium channels, and activating calcium-dependent signalling proteins that control insulin exocytosis.

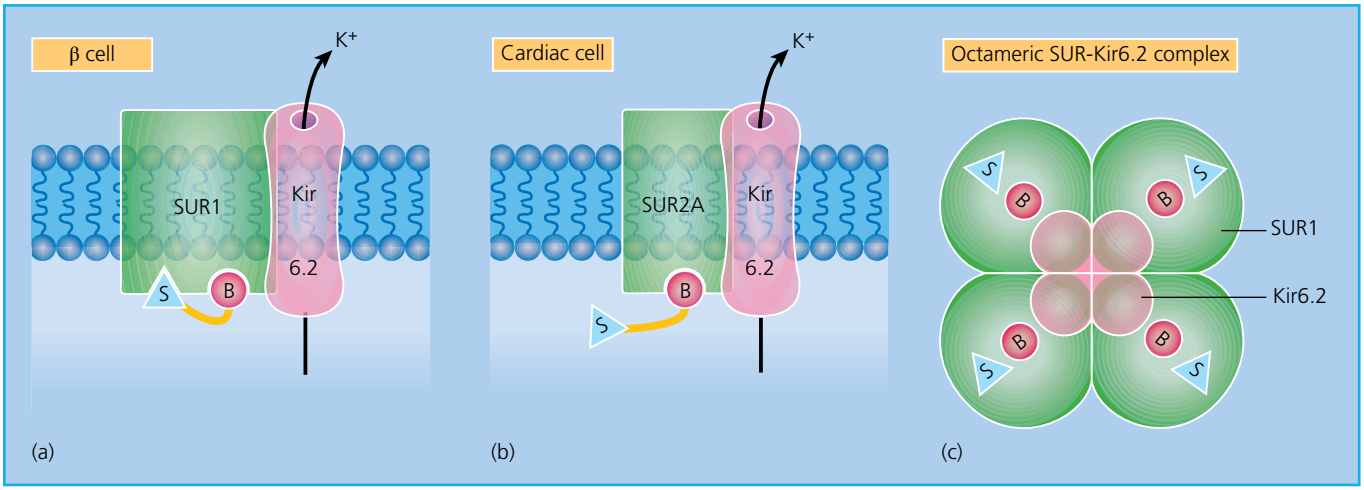

Figure 35.8 (a) The transmembrane complex of the SUR1 sulfonylurea receptor and the ATP-sensitive Kir6.2 potassium efflux channel on the pancreatic β cells. Each SUR1 has a cytosolic sulfonylurea (S) binding site and a benzamido (B) binding site. (b) SUR2A on cardiac muscle cells (and SUR2B on vascular smooth muscle cells) does not have a sulfonylurea binding site. (c) The SUR1–Kir6.2 complex is a non-covalently bonded octamer comprising 4 × SUR1 and 4 × Kir6.2, illustrated from the cytosolic surface to show the sulfonylurea and benzamido binding sites. The Kir6.2 components are located at the centre and form the K^+ efflux pore. The Kir6.2 channel has a cytosolic binding region for ADP/ATP.

Table 35.7 Sulfonylureas.

Agent[a]	Dose range (mg/day)	Duration of action (h)	Metabolites	Elimination
Tolbutamide	500–2000	6–10	Inactive	Urine 100%
Glipizide	2.5–20	6–16	Inactive	Urine ~70%
Gliclazide	40–320	12–20	Inactive	Urine ~65%
Gliclazide MR	30–120	18–24	Inactive	Urine ~65%
Glimepiride	1.0–6.0	12–>24	Active	Urine ~60%
Glibenclamide[b]	1.25–15	12–>24	Active	Bile >50%
Chlorpropamide[c]	100–500	24–50	Active	Urine >90%

MR, modified release.
[a] People with newly diagnosed type 2 diabetes are not usually started on first-generation sulfonylureas (tolbutamide, chlorpropamide).
[b] Glibenclamide is also known as glyburide in some countries.
[c] Chlorpropamide is no longer available in many countries.

threshold for glucose-stimulated insulin release (~5 mmol/l), they are capable of causing hypoglycaemia, mainly through insulin-induced suppression of hepatic glucose production.

Sulfonylureas may exert minor glucose-lowering effects independently of increased insulin secretion [40, 41]. A small reduction in glucagon concentrations, increased peripheral glucose transport, and increased hepatic glucose deposition have been reported, but these effects are not considered to be of sufficient magnitude to be clinically relevant.

Pharmacokinetics

Sulfonylureas vary considerably in their pharmacokinetic properties (Table 35.7), which in turn affects their clinical suitability for different individuals [40–42]. They are generally well absorbed, and reach peak plasma concentration in 2–4 hours. Sulfonylureas are highly bound to plasma proteins, which can lead to interactions with other protein-bound drugs such as salicylates, sulfonamides, and warfarin. Also, displacement of protein-bound sulfonylurea can increase the risk of hypoglycaemia (Table 35.5). Sulfonylureas are metabolized in the liver to varying extents to a range of active and inactive metabolites that are eliminated along with unchanged drug via the bile and urine. Longer-acting sulfonylureas can be given once daily but carry a greater risk of hypoglycaemia, especially with active metabolites. Sites and rates of metabolism and elimination are also important considerations, especially in older people and individuals with coexisting liver or kidney disease or taking several other medications.

The formulation of some sulfonylureas has been altered to modify the duration of action. For example, a micronized formulation of glibenclamide (termed glyburide) in the USA increases the rate of gastrointestinal absorption for earlier onset of action. A longer-acting (extended-release) formulation of glipizide and a modified-release (MR) formulation of gliclazide have been introduced for once-daily dosing. Interestingly, the 30 mg preparation of gliclazide MR gives similar efficacy to 80 mg of unmodified gliclazide and reduces the risk of severe hypoglycaemia [43].

Indications and contraindications

Sulfonylureas are widely used as monotherapy and in combination with metformin or a thiazolidinedione. They can also be used with an α-glucosidase inhibitor or SGLT-2 inhibitor, and there are individuals who can benefit from a combination of a sulfonylurea with an incretin agent or insulin. Combination of a sulfonylurea with a different type of glucose-lowering agent usually affords approximately additive glucose-lowering efficacy, at least initially, but there is an increased risk of hypoglycaemia. The additive efficacy of a sulfonylurea with another type of insulin secretagogue is dependent on different modes of action on the β cell.

The pharmacological theory of adding a sulfonylurea (or other insulin secretagogue) to insulin therapy for people with type 2 diabetes is that subcutaneous insulin injections do not mimic the normal endogenous delivery of more insulin to the liver than to the periphery. Thus, where there is residual endogenous β-cell function, a stimulus to increase delivery of endogenous insulin to the liver should assist in reducing hepatic glucose production,

particularly during digestion of a meal. Hence daytime sulfonylurea is sometimes given with bedtime insulin, and this can substantially, if only temporarily, reduce the required insulin dose [40,42]. Guidelines generally include sulfonylureas as alternative first-line oral therapy where metformin is not appropriate or not tolerated, although DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists are generally favoured in recent guidelines. Because sulfonylurea therapy is associated with weight gain, these agents have customarily been preferred for people who are not overweight.

Sulfonylurea therapy is begun with a low dose, preferably with self-monitoring of blood glucose by the individual at least once daily during the first few weeks. This is especially recommended where there are strong concerns about the potential consequences of hypoglycaemia (e.g. in older individuals and those living alone, operating machinery, or driving). In general, people who have responded to some extent (but still inadequately) with lifestyle measures and have less marked fasting hyperglycaemia are more likely to incur hypoglycaemia with a sulfonylurea. The dosage is uptitrated at 2–4-week intervals as required. Hypoglycaemia or early hypoglycaemic symptoms are the main limitation to dose escalation of sulfonylureas. If evidence of hypoglycaemia occurs before the glycaemic target is achieved, or if a dosage increment produces no further glycaemic benefit, it is advisable to return to the previous dose. Adjustment of the administration regimen may assist or an alternative class of insulin secretagogue may be more suitable. Where the sulfonylurea is taken as monotherapy and the glycaemic target is not achieved, then addition of an agent to reduce insulin resistance or an SGLT-2 inhibitor or an α-glucosidase inhibitor is the usual recourse. Note that the maximal blood glucose-lowering effect of a sulfonylurea is usually achieved at a dose that is well below the recommended maximum, indicating that maximal stimulation of insulin secretion has already been achieved.

Efficacy

As monotherapy in people whose diabetes is inadequately managed by lifestyle measures, sulfonylureas can be expected to reduce fasting plasma glucose by about 2–4 mmol/l, equating to a decrease in HbA_{1c} of 1–2% (11–22 mmol/mol) [2,5,40–43]. The glucose-lowering effect of sulfonylureas is immediate, and they are particularly effective in the short term. Efficacy is dependent, however, on sufficient reserve of β-cell function, and this is set against the inevitable decline in β-cell function as the natural history of type 2 diabetes proceeds. Hence it is expected that the dose will need to be escalated to counter the progressive loss of β-cell function, which can reduce the durability of the glucose-lowering efficacy. A rapid deterioration of glycaemic indices during sulfonylurea therapy (sometimes termed *secondary sulfonylurea failure*) occurs in ~5–10% of people per annum. Although this may possibly vary between compounds, it largely reflects the progression of β-cell failure [2,5,40–43]. Early intervention in people with a greater reserve of β-cell function usually produces a better and longer response to sulfonylureas, although not without risk of hypoglycaemia, whereas late intervention in those with severely compromised β-cell function is less effective.

Sulfonylureas generally have little effect on blood lipids. Occasionally, their use will cause a small decrease in plasma triglyceride or increase in HDL cholesterol.

Adverse effects

Weight gain, typically in the range 1–4 kg, is common after initiation of sulfonylurea therapy; it stabilizes by about six months [40–42]. The weight gain probably reflects the anabolic effects of increased plasma insulin concentrations together with reduced loss of glucose in the urine.

Hypoglycaemia is a common and potentially the most serious adverse effect of sulfonylurea therapy. Although it is only rarely life threatening in people with type 2 diabetes, even mild impairment of neural or motor function can endanger the individual and others, and may predispose to a poor prognosis after a myocardial infarction [44]. People treated with sulfonylureas should be given instruction on the prevention and recognition of hypoglycaemia and the prompt actions required. In the UKPDS, ~20% of sulfonylurea-treated participants reported one or more episodes of hypoglycaemic symptoms annually. Other studies have suggested similar rates [9,12,42]. Severe hypoglycaemia (requiring third-party assistance) during sulfonylurea therapy occurred in ~1% of participants annually in the UKPDS, and lower rates (~0.2–2.5 episodes per 1000 patient-years) have been reported elsewhere. The mortality risk from sulfonylurea-induced hypoglycaemia is reported to be 0.014–0.033 per 1000 patient-years [44]. Longer-acting sulfonylureas, irregular meals, combination with other glucose-lowering drugs, especially insulin, excessive alcohol consumption, already near-normal fasting glycaemia, old age, and interacting drugs can predispose to an increased risk of hypoglycaemia.

Sulfonylurea-induced hypoglycaemia requires prompt admission to hospital. Treatment with glucose by continuous intravenous infusion, probably for more than one day, is applied to guard against the tendency for a recurrence of hypoglycaemia where long-acting sulfonylureas are concerned. If accumulation of chlorpropamide is suspected, renal elimination may be enhanced by forced alkaline diuresis. The vasodilator diazoxide and the somatostatin analogue octreotide have been used successfully (but with extreme caution) to inhibit insulin secretion in severe sulfonylurea-induced hypoglycaemia. Use of glucagon in people with type 2 diabetes should be avoided as this is itself an insulin secretagogue.

Very occasionally, sulfonylureas produce sensitivity reactions, usually transient cutaneous rashes. Erythema multiforme is rare. Fever, jaundice, acute porphyria, photosensitivity, and blood dyscrasias are also rare. Chlorpropamide (no longer in common use) was known for its propensity to cause facial flushing with alcohol and increasing renal sensitivity to antidiuretic hormones, occasionally causing water retention and hyponatraemia. Glibenclamide is claimed to have a mild diuretic action.

Although the efficacy of sulfonylureas depends on the stimulation of insulin secretion, this seldom raises plasma insulin concentrations beyond the range of normal individuals without diabetes and those with IGT. The suggestion emanating from the University Group Diabetes Program study in the 1960s that tolbutamide-induced hyperinsulinaemia might have a detrimental effect on the cardiovascular system remains unsubstantiated.

Further studies on the cardiovascular safety of sulfonylureas were prompted by the finding that two isoforms of the sulfonylurea receptor, SUR2A and SUR2B, are expressed in cardiac muscle and vascular smooth muscle, respectively. These isoforms lack the sulfonylurea binding site, but they retain the benzamido binding site (Figure 35.8). Therefore, SUR2A/B can only bind those sulfonylureas that contain a benzamido group (glibenclamide, glipizide, glimepiride) [37]. Sulfonylureas without a benzamido group (e.g. tolbutamide, chlorpropamide, gliclazide) show very little interaction with the cardiac and vascular SUR receptors. The effects of the K^+ATP channel opener nicorandil (an anti-anginal drug with cardioprotective properties) are blocked by sulfonylureas that have a benzamido group. Compounds with a benzamido group could

theoretically interfere with ischaemic preconditioning and increase vascular contractility at a time when this might be undesirable (e.g. severe myocardial ischaemia). However, there is no clear evidence that therapeutic concentrations of sulfonylureas exert such an effect. Indeed, hyperglycaemic states appear to obviate ischaemic preconditioning, but some authorities continue to advocate that the use of sulfonylureas is kept to a minimum in people with overt coronary artery disease [41,45].

Meglitinides (short-acting prandial insulin releasers)

Meglitinide analogues (sometimes termed glinides) were evaluated as potential glucose-lowering agents after an observation in the 1980s that meglitinide – the non-sulfonylurea moiety of glibenclamide that contains the benzamido group – could stimulate insulin secretion similarly to a sulfonylurea [46]. The pharmacokinetic properties of these compounds favoured a rapid but short-lived insulin secretory effect that suited administration with meals to promote prandial insulin release. By generating a prompt increase of insulin to coincide with meal digestion, these agents help to restore partially the first-phase glucose-induced insulin response that is lost in type 2 diabetes. Specifically targeting post-prandial hyperglycaemia might also address the vascular risk attributed to prandial glucose excursions and reduce the risk of inter-prandial hypoglycaemia [47]. Two agents, the meglitinide derivative repaglinide and the structurally related phenylalanine derivative nateglinide, were introduced in 1998 and 2001, respectively, as *prandial insulin releasers* (Figure 35.9). Although acting mainly during the prandial and early post-prandial periods, their effects extend sufficiently to produce some reduction of fasting hyperglycaemia, particularly with repaglinide.

Mode of action

Prandial insulin releasers bind to the benzamido site on the sulfonylurea receptor SUR1 in the plasma membrane of the islet β cells (Figure 35.8). This site is distinct from the sulfonylurea site, but the response to binding is the same as for sulfonylureas, causing closure of the K^+ATP channel. Thus, there is usually no therapeutically additive advantage of using the two types of agents together.

Pharmacokinetics

Repaglinide is almost completely and rapidly absorbed with peak plasma concentrations after about one hour. It is quickly metabolized in the liver to inactive metabolites, which are mostly excreted in the bile (Table 35.8). Taken about 15 minutes before a meal,

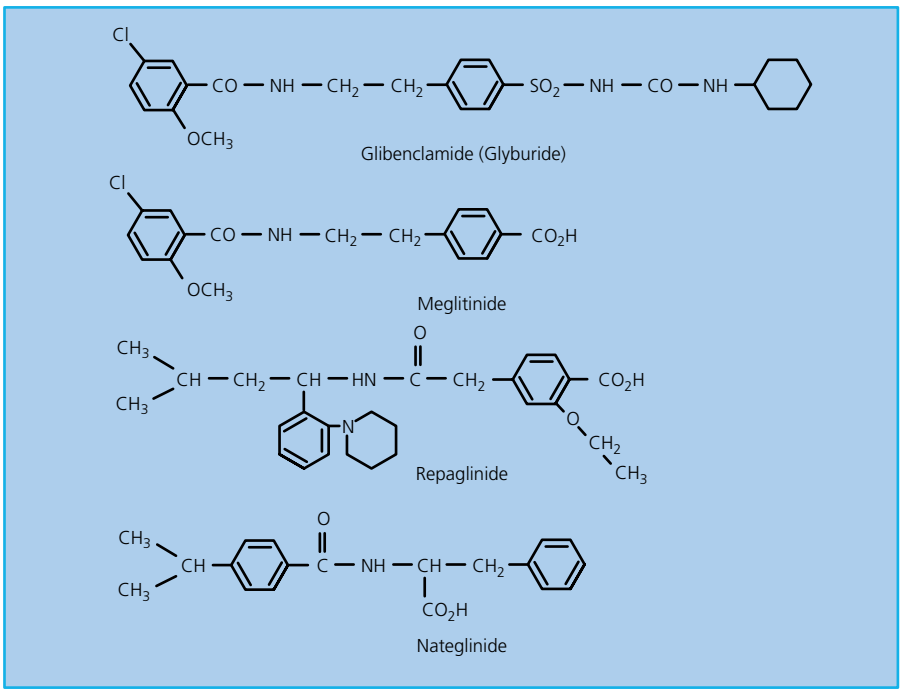

Figure 35.9 Chemical structures of meglitinide and the prandial insulin releasers repaglinide and nateglinide compared with glibenclamide (glyburide).

Table 35.8 The meglitinides: repaglinide and nateglinide.

Agent	Dose range (mg/meal)	Maximum daily dose (mg)	Duration of action (h)	Metabolites	Elimination
Repaglinide	0.5–4.0	16	4–6	Inactive	Bile ~90%
Nateglinide	60–180	540	3–5	One slightly active	Urine ~80%

repaglinide produces a prompt insulin response that lasts about three hours, coinciding with the duration of meal digestion. Nateglinide has a slightly faster onset and shorter duration of action [47].

Indications and contraindications

Prandial insulin releasers can be used as monotherapy in people whose diabetes is inadequately managed by non-pharmacological measures. They are perhaps most suited for individuals who exhibit post-prandial glycaemic excursions while retaining near-normal fasting glycaemia. As rapid-acting insulin releasers, they can be helpful to individuals with irregular lifestyles with unpredictable or missed meals. The lower risk of hypoglycaemia also provides a useful option for some older individuals, particularly if other agents are contraindicated, although the need for multiple daily dosages may be a disincentive.

Repaglinide is ideally taken 15–30 minutes before a meal. Therapy is introduced with a low dose (e.g. 0.5 mg) and glycaemic levels are monitored during titration every two weeks up to a maximum of 4 mg before each main meal. When a meal is not consumed, the corresponding dose of repaglinide should be omitted. With appropriate caution and monitoring, repaglinide can be given to those with moderate renal impairment where some sulfonylureas and metformin are contraindicated.

Nateglinide can be used as monotherapy in much the same way as repaglinide, although nateglinide tends to be faster and shorter acting and requires caution in people with hepatic disease. Note that in some countries, such as the UK, nateglinide is not licensed for use as monotherapy, only for combination therapy.

If the desired glycaemic target is not met with a prandial insulin releaser, early introduction of combination therapy (e.g. with an agent to reduce insulin resistance) can be considered. Prandial insulin releasers can also be useful add-ons to monotherapy with metformin or a thiazolidinedione.

Efficacy

Consistent with their use to boost prandial insulin secretion, repaglinide (0.5–4 mg) and nateglinide (60–180 mg) taken before meals produce dose-dependent increases in insulin concentrations and reduce post-prandial hyperglycaemia. There is usually a small reduction in fasting hyperglycaemia. Reductions in HbA_{1c} are similar to or smaller than with sulfonylureas, as predicted by their shorter duration of action. As an add-on to metformin, they can reduce HbA_{1c} by an additional 0.5–1.5% (6–17 mmol/mol).

Adverse effects

Hypoglycaemic episodes are fewer and less severe with prandial insulin releasers than with sulfonylureas. Sensitivity reactions, usually transient, are uncommon. Plasma levels of repaglinide may be increased during co-administration with gemfibrozil. Prandial insulin releasers may cause a small increase in body weight when started as initial monotherapy, but body weight is little affected among people switched from a sulfonylurea or when a prandial insulin releaser is combined with metformin.

Thiazolidinediones

The glucose-lowering activity of a thiazolidinedione (ciglitazone) was reported in the early 1980s. In the early 1990s, the peroxisome proliferator-activated receptor (PPAR) family was identified as part of the nuclear receptor superfamily 1, and it became evident that thiazolidinediones were potent agonists of PPAR-γ [48]. The PPAR-γ-mediated transcriptional effects of thiazolidinediones improved whole-body insulin sensitivity, and troglitazone became the first thiazolidinedione to enter routine clinical use, introduced in the USA in 1997. The drug, however, was associated with fatal cases of idiosyncratic hepatotoxicity and was withdrawn in 2000. Troglitazone was available for only a few weeks in 1997 in the UK. Two other thiazolidinediones, rosiglitazone and pioglitazone (Figure 35.10), which did not show hepatotoxicity, were introduced in the USA in 1999 and in Europe in 2000. Fixed-dose combinations of each agent with metformin also became available.

By 2007, meta-analyses of safety data for rosiglitazone were indicating increased risks of heart failure, myocardial infarction, and cardiovascular death, resulting in withdrawal of rosiglitazone in Europe in 2010 and restricted use in the USA (placement on Risk Evaluation and Mitigation Strategy, REMS) [49]. However, evaluation of a large prospective cardiovascular outcome study with rosiglitazone (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes, RECORD) did not confirm the increased risk of myocardial infarction and cardiovascular death, and the REMS restriction in the USA was lifted in 2013. An earlier study in 2007 with pioglitazone (Prospective Pioglitazone Clinical Trial in Macrovascular Events, PROactive) had not shown increased risk of myocardial infarction or cardiovascular death, and pioglitazone has since been shown to reduce risk of stroke [50,51]. However, concerns regarding weight gain, oedema, risk of bone fracture, and other potential cautions have limited the use of pioglitazone in some countries [5].

Mode of action

Most of the glucose-lowering efficacy of thiazolidinediones appears to be achieved through stimulation of PPAR-γ, leading to increased insulin sensitivity [5,48,52]. PPAR-γ is highly expressed in adipose tissue, and to a lesser extent in muscle and liver. When activated it forms a heterodimeric complex with the retinoid X receptor and binds to a nucleotide sequence (AGGTCAXAGGTCA) termed the peroxisome proliferator response element (PPRE) located in the promoter regions of PPAR-responsive genes. In conjunction with co-activators such as PGC-1, this alters the transcriptional activity of a range of insulin-sensitive and other genes (Table 35.9). Many of these genes participate in lipid and carbohydrate metabolism (Figure 35.11). Stimulation of PPAR-γ by a thiazolidinedione promotes differentiation of pre-adipocytes into mature adipocytes; these new small adipocytes, mostly in subcutaneous depots, are particularly sensitive to insulin, and show increased uptake of fatty acids with increased lipogenesis. This in turn reduces circulating

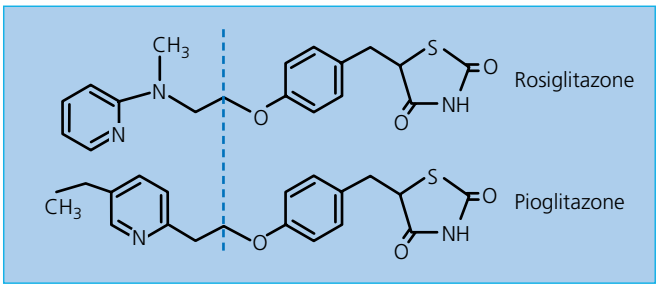

Figure 35.10 Chemical structures of thiazolidinediones rosiglitazone and pioglitazone.

Table 35.9 Examples of key genes activated by thiazolidinediones via stimulation of the peroxisome proliferator-activated receptor γ (PPAR-γ).

↑ Lipoprotein lipase
↑ Fatty acid transporter protein (FATP/CD36)
↑ Adipocyte fatty acid-binding protein (aP2)
↑ Acyl-CoA synthetase
↑ Malic enzyme
↑ Glycerol kinase (in adipocytes?)
↑ PEPCK (adipocytes), ↑ perilipin
↑ GLUT4 (by derepression), ↑ GLUT2 (islet β cells)
↓ 11β-Hydroxysteroid dehydrogenase-1
↓ Resistin, ↓ RBP 4
↑ Adiponectin (↑ leptin?)
↓ TNF-α, ↓ IL-6
↓ CRP and some proinflammatory cytokines, ↓ NFκB
↓ PAI-1, ↓ MMP-9
↑ UCP-1 (?)

Not all genes appear to be activated in all tissues due in part to the involvement of different coactivators in different tissues. The main effects are in adipose tissue.
↑, Increase expression; ↓, decrease expression; ?, unconfirmed. CRP, C-reactive protein; GLUT, glucose transporter; IL-6, interleukin 6; MMP-9, matrix metalloproteinase 9; NFκB, nuclear factor κB; PAI-1, plasminogen activator inhibitor 1; PEPCK, phosphoenolpyruvate carboxy kinase; RBP, retinol-binding protein; TNF-α, tumour necrosis factor α; UCP-1, uncoupling protein 1.

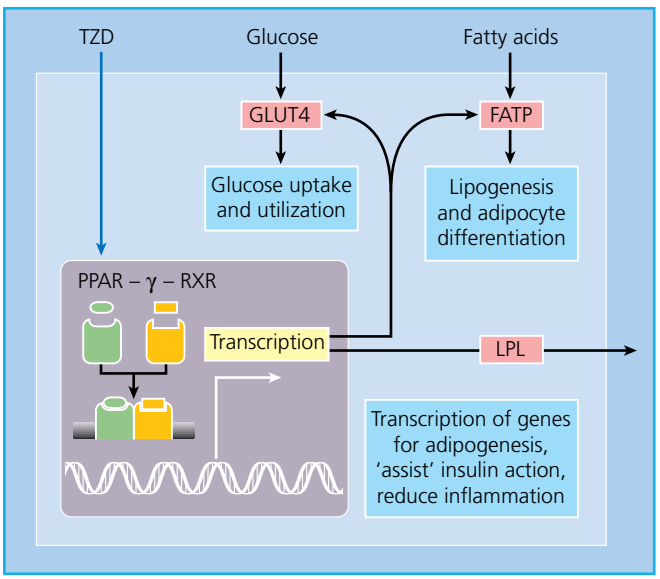

Figure 35.11 Mechanism of action of thiazolidinediones. Most actions of a thiazolidinedione (TZD) are mediated via stimulation of the nuclear peroxisome proliferator-activated receptor γ (PPAR-γ), which is highly expressed in adipose tissue. When stimulated, PPAR-γ forms a heterodimeric complex with the retinoid X receptor (RXR). The complex binds to the peroxisome proliferator response element (PPRE) nucleotide sequence (AGGTCAXAGGTCA) in the promoter regions of certain genes, recruits co-activators, and alters the transcriptional activity of these genes. This modifies nutrient uptake and metabolism, and also the other functions of the cell.

non-esterified (free) fatty acids, which rebalances the glucose–fatty acid (Randle) cycle, facilitating glucose utilization and restricting fatty acid availability as an energy source for hepatic gluconeogenesis. By reducing circulating fatty acids, ectopic lipid deposition in muscle and liver is reduced, which further contributes to improvements of glucose metabolism. Thiazolidinediones also increase mitochondrial biogenesis, but may act directly on mitochondria to reduce respiratory function.

Thiazolidinediones increase glucose uptake into adipose tissue and skeletal muscle via increased availability of GLUT4 glucose transporters. Improvements in insulin sensitivity are likely to be assisted by reduced production of several adipocyte-derived pro-inflammatory cytokines, notably tumour necrosis factor α (TNF-α), which is implicated in muscle insulin resistance. Thiazolidinediones also increase the production of adiponectin, which enhances insulin action and exerts potentially beneficial effects on vascular reactivity. Because PPAR-γ is expressed to a small extent in many tissues, thiazolidinediones can affect responsive genes at these locations, and this has given rise to the tag *pleiotropic effects* [52,53].

Thiazolidinediones, like metformin, require the presence of sufficient insulin to generate their blood glucose–lowering effect. Plasma insulin concentrations are typically lowered by thiazolidinediones, and long-term viability of islet β cells might be improved [53].

Pharmacokinetics

Absorption of rosiglitazone and pioglitazone is rapid and almost complete, with peak concentrations at 1–2 hours, but slightly delayed when taken with food. Both drugs are metabolized extensively by the liver. Pioglitazone is metabolized predominantly by CYP2C8 and CYP3A4 to active metabolites that are eliminated in the bile (Table 35.10). Pioglitazone does not cause any clinically significant reductions in plasma concentrations of other drugs metabolized by CYP3A4, such as oral contraceptives. Both thiazolidinediones are almost completely bound to plasma proteins, but their concentrations are not sufficient to interfere with other protein-bound drugs.

Indications and contraindications

Thiazolidinediones can be used as monotherapy in individuals with type 2 diabetes with and without obesity in whom lifestyle does not afford adequate glycaemic levels. Various treatment algorithms ascribe different positions for thiazolidinediones, but in general they can be used as monotherapy if metformin is inappropriate or not tolerated, and as an add-on to metformin for those in whom weight gain is not an issue and an insulin secretagogue is not favoured. Because of their slow onset of action, it is not straightforward to substitute a thiazolidinedione for another class of glucose-lowering agent without a temporary deterioration in glycaemic levels. Combination of a thiazolidinedione with insulin can improve

Table 35.10 The thiazolidinediones: pioglitazone and rosiglitazone.

Agent	Dose range (mg/day)	Duration of action (h)	Metabolites	Elimination
Pioglitazone	15–45	~24	Active	Bile >60%
Rosiglitazone	4–8	~24	Inactive	Urine ~64%

glycaemic indices while reducing insulin dosages, especially in individuals with obesity, but requires extra caution as peripheral oedema is more common [53].

The propensity for fluid retention with thiazolidinediones, which can increase plasma volume by up to 500 ml, reduce haematocrit, and decrease the haemoglobin concentration up to 1 g/dl, contraindicates these agents for people with evidence of heart failure. The exclusion criteria, based on cardiac status, vary between countries; for example, New York Heart Association classes I–IV are exclusions in Europe, whereas classes III and IV are exclusions in the USA [5]. Appropriate clinical monitoring is important, especially for people considered at higher risk for cardiac failure and those showing marked initial weight gain. Despite an increased fluid volume, thiazolidinediones do not increase, and usually slightly decrease, blood pressure.

The troglitazone experience of idiosyncratic hepatotoxicity prompted vigilance with liver function by measuring serum alanine aminotransferase (ALT) before starting rosiglitazone and pioglitazone therapy, and periodically thereafter. Pre-existing liver disease, development of clinical hepatic dysfunction, or elevated ALT levels >2.5 times the upper limit of normal are contraindications to thiazolidinediones. Interestingly, because of the effects of thiazolidinediones to reduce hepatic fat, recent studies have suggested that this class of drug might be useful for the treatment of non-alcoholic steatohepatitis [53].

If there are no contraindications, a thiazolidinedione can be used in older people. A thiazolidinedione can also be considered for individuals with mild renal impairment, while appreciating the potential for oedema. Use of a thiazolidinedione in women with anovulatory PCOS can cause ovulation to resume, but thiazolidinediones should not be continued in pregnancy.

Efficacy

Thiazolidinediones produce a slowly generated anti-hyperglycaemic effect, which usually requires 2–3 months to reach maximum effect [52, 53]. This tends to prolong the dose titration process, and because the therapeutic response can vary considerably between individuals, it is appropriate to consider the individual as a non-responder and to switch to another treatment if there is no clinically meaningful effect after three months. Thiazolidinediones reduce HbA_{1c} by around 0.5–1.5% (6–17 mmol/mol). In a long-term monotherapy comparison with metformin or a sulfonylurea (A Diabetes Outcome Progression Trial, the ADOPT study), rosiglitazone showed a slower onset but more durable glucose-lowering effect over more than three years [54]. The effect of thiazolidinediones may be better in people with greater β-cell reserve and in more overweight individuals, but a clear indicator of the best responders has not been established. Thiazolidinediones do not cause hypoglycaemia as monotherapy.

Thiazolidinediones substantially reduce circulating non-esterified (free) fatty acids, but effects on other components of the plasma lipid profile have been the subject of debate. Rosiglitazone tends to cause a small rise in the total cholesterol concentration, which stabilizes by about three months, although this may be mitigated by adequate statin therapy. The effect appears to reflect a rise in both LDL and HDL cholesterol, leaving the LDL-to-HDL cholesterol ratio and the total-to-HDL cholesterol ratio little changed or slightly improved. Pioglitazone generally appears to have little effect on total cholesterol, and has frequently reduced triglyceride concentrations in clinical trials. Both thiazolidinediones reduce the proportion of the smaller, denser (more atherogenic) LDL particles [53].

Weight gain, similar in magnitude to sulfonylurea therapy (typically 1–4 kg) and stabilizing over 6–12 months, is usually observed after initiation of thiazolidinedione therapy. Several studies indicate that the distribution of body fat is altered; the visceral adipose depot is little changed or reduced, while the subcutaneous depot is increased as new small, insulin-sensitive adipocytes are formed [53].

Thiazolidinediones exert beneficial effects on a selection of atherothrombotic risk markers, indices of vascular reactivity, and components of the metabolic syndrome. For example, thiazolidinediones downregulate PAI-1 expression, decrease urinary albumin excretion to a greater extent than expected for the improvement in glycaemic levels, reduce cIMT and coronary restenosis, and reduce circulating markers of chronic low-grade inflammation [53]. However, a recent pragmatic trial (Thiazolidinediones Or Sulfonylureas and Cardiovascular Accidents. Intervention Trial, TOASCA.IT) noted that the incidence of cardiovascular events was similar when either pioglitazone or a sulfonylurea was added to metformin [55]. Thiazolidinediones also reduce the occurrence of new-onset diabetes in individuals with IGT or those with a history of gestational diabetes [53].

Adverse effects

Despite improvements in several atherothrombotic risk factors, the main concerns over thiazolidinediones have focused on the cardiovascular impact of oedema, reduced haemoglobin levels, and congestive heart disease. Although long-term cardiovascular events were reduced during a large prospective study with pioglitazone (PROactive), the cardiovascular safety issues raised over rosiglitazone reduced confidence in the class, and the TOSCA.IT pragmatic study indicated no overall cardiovascular benefit of pioglitazone [49, 50, 53, 55].

Recent studies have noted an approximate doubling of the risk of a bone fracture with use of a thiazolidinedione, mainly at distal sites and among postmenopausal women [53]. This has been attributed at least in part to a reduction in bone mineral density. Stimulation of PPAR-γ in colonic cells has been reported both to increase and to decrease the risk of tumours in animals and cell models; thus, familial polyposis coli is a contraindication to thiazolidinediones on theoretical grounds. There has been debate concerning a possible increased risk of bladder cancer with pioglitazone, and the drug is not recommended for people with active bladder disease or a history of bladder disease. However, long-term safety analyses have not confirmed a significant increase in risk of bladder cancer with pioglitazone [53].

Hypoglycaemia may occur several weeks after adding a thiazolidinedione to a sulfonylurea; self-monitoring of blood glucose can be helpful to identify when the dosage of the sulfonylurea should be reduced.

Dipeptidyl peptidase 4 inhibitors

DPP-4 inhibitors (often termed gliptins) inhibit the enzyme DPP-4, which is responsible for the rapid degradation of two key incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1). Thus DPP-4 inhibitors enhance endogenous incretin activity by preventing the rapid degradation of these incretin hormones. The history, structure, and function of incretin hormones, and the therapeutic role of subcutaneously injected GLP-1 receptor agonists such as exenatide,

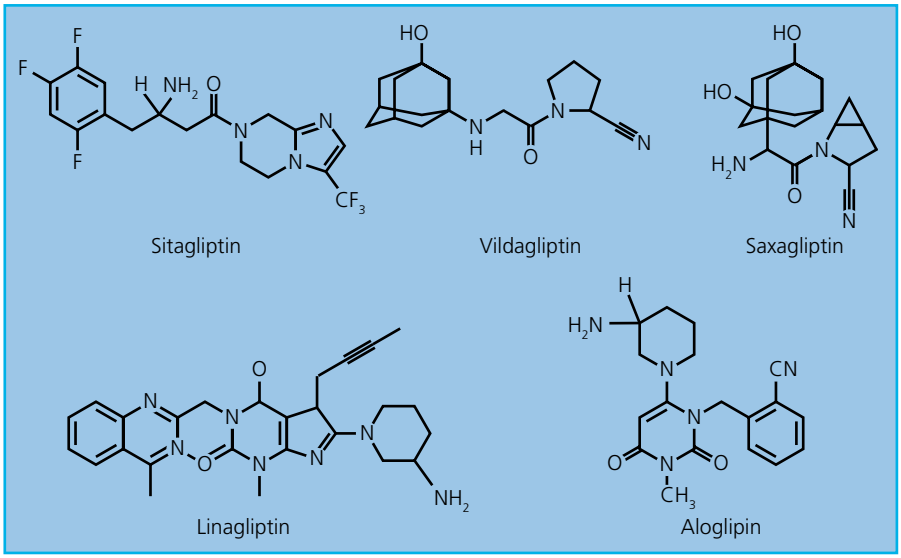

Figure 35.12 Chemical structures of the dipeptidyl peptidase 4 (DPP-4) inhibitors (gliptins) sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin.

liraglutide, lixisenatide, and dulaglutide, are covered in Chapter 36. Briefly, incretin hormones are secreted from the intestine in response to meal digestion; one of their main actions is to increase glucose-induced insulin secretion by the pancreatic islet β cells, thereby reducing prandial glucose excursions [5, 56, 57]. GLP-1 also suppresses glucagon secretion from the islet α cells, exerts a satiety effect, and delays gastric emptying.

It was noted in the 1980s that the incretin effect is reduced in type 2 diabetes, and subsequent studies have shown that this is largely due to reduced activity of GLP-1 [58, 59], suggesting that administration of extra GLP-1 might be therapeutically useful. Because GLP-1 is rapidly degraded ($t_{1/2}$ <2 minutes) by DPP-4, the potential of DPP-4 inhibitors was investigated in the 1990s, giving rise to the introduction of several specific inhibitors [60], notably sitagliptin (2007), vildagliptin (2008), saxagliptin (2008), linagliptin (2011), and alogliptin (2013) (Figure 35.12).

Mode of action

DPP-4 inhibitors act to prevent the aminopeptidase activity of DPP-4; the enzyme is found free in the circulation and tethered to endothelia and other epithelial cells in most tissues, especially in the intestinal mucosa [61]. DPP-4 cleaves the N-terminal dipeptide from peptides that have either an alanine or a proline residue penultimate to the N-terminus. The incretins GLP-1 and GIP are prime targets for DPP-4, and DPP-4 inhibitors more than double their circulating concentrations (although this is not as high as the concentrations of subcutaneously administered GLP-1 receptor agonists) [58]. Raised endogenous incretin concentrations enhance nutrient-induced insulin secretion. Increased insulin biosynthesis and increased β-cell mass have also been noted in some animal studies, but these effects have not been confirmed in clinical studies (Table 35.11). Increased GLP-1 concentrations also suppress excessive glucagon secretion. Because these effects are glucose dependent, there is a low risk of inducing significant hypoglycaemia, and this is a key reason for the increased use of DPP-4 inhibitors in preference to sulfonylureas. The elevation of GLP-1 levels produced by DPP-4 inhibitors is not generally sufficient to create a measurable satiety effect or sufficient to delay gastric emptying, hence avoiding any nausea. Body weight is usually little changed or slightly reduced by DPP-4 inhibitors (Figure 35.13).

Table 35.11 Effects of the incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) on glucose homeostasis.

	GLP-1	GIP
Effects on pancreatic islets		
Increase nutrient-induced insulin secretion	✓	✓
Increase insulin biosynthesis[a]	✓	✓
Increase β-cell mass[a]	✓	✓
Suppress glucagon secretion	✓	–
Increase somatostatin secretion	✓	–
Extrapancreatic effects		
Slow/delay gastric emptying	✓	–
Decrease gastric acid secretion	–	✓
Promote satiety and weight reduction	✓	–
Promote lipogenesis	–	✓

✓, Yes; –, no effect.
[a] Effect observed in animal studies but not confirmed by clinical studies in type 2 diabetes.

Because the incretin-mediated effect of DPP-4 inhibitors potentiates glucose-dependent insulin secretion, the activity period of these agents is mostly prandial. Although they are particularly effective in lowering post-prandial hyperglycaemia, there is a substantial carryover effect to benefit inter-prandial glycaemia [58, 60, 61]. By contrast, DPP-4 inhibitors do not initiate insulin secretion and so they do not increase basal insulin secretion. Also, they only suppress glucagon secretion in the hyperglycaemic state, and so there is a low risk of inter-prandial overshoot into hypoglycaemia.

Pharmacokinetics

The pharmacokinetic properties of DPP-4 inhibitors are summarized in Table 35.12. DPP-4 inhibitors are selective, competitive, and reversible inhibitors of DPP-4 (IC_{50} in the lower nmol/l range). They mimic the N-terminal dipeptide structure of the incretins, which enables them to block the catalytic site of DPP-4 through either covalent (vildagliptin and saxagliptin) or non-covalent

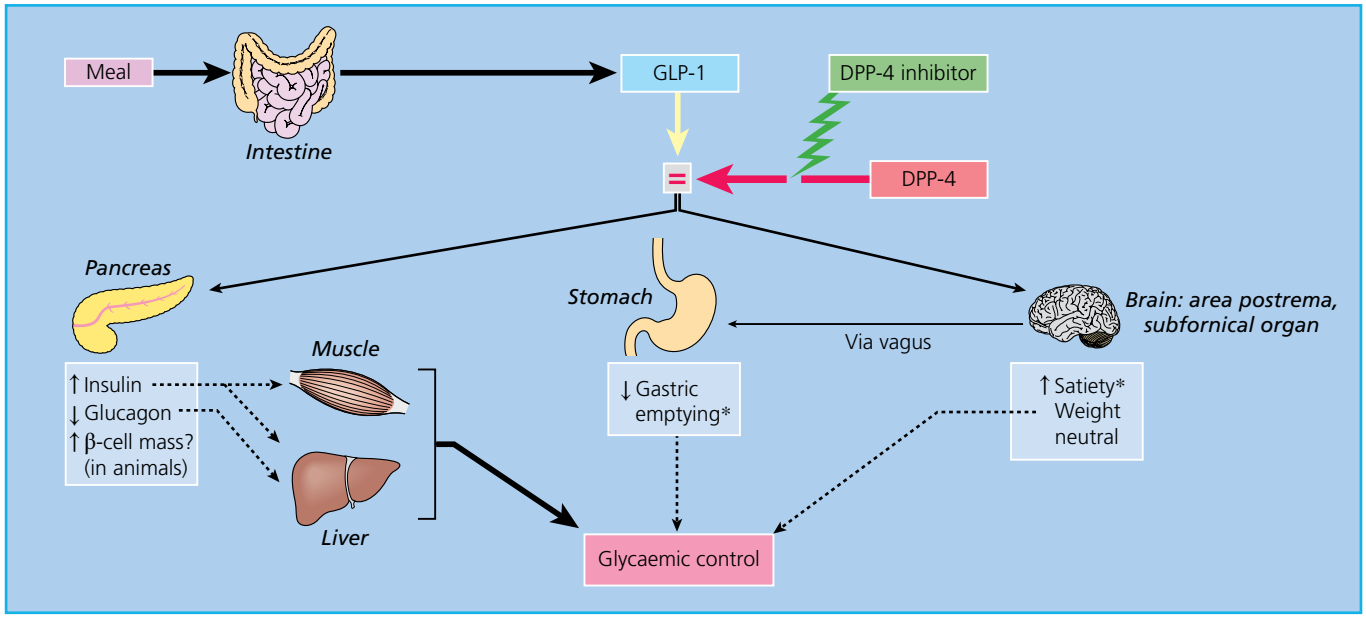

Figure 35.13 Sites of action of dipeptidyl peptidase 4 (DPP-4) inhibitors (gliptins). Incretin hormones such as glucagon-like peptide-1 (GLP-1) are released in response to a meal. These hormones are normally degraded rapidly by the enzyme DPP-4. Inhibiting DPP-4 allows the normal effects of the incretin hormones to be enhanced. The main site of the enhanced incretin effect is on the pancreas to increase nutrient-induced insulin secretion. GLP-1 also reduces glucagon secretion. *Potential effects to slow gastric emptying and increase satiety probably contribute little to the therapeutic efficacy of DPP-4 inhibitors.

Table 35.12 Dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins): sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin.

Agent	od/bd[a]	Dose (mg/d)	$t_{1/2}$ (h)	IC_{50} (nM)[b]	Selectivity for DPP4[c]	Metabolism	Excretion
Sitagliptin	od	100	8–24	19	>2500	Unchanged	Urine ~80%
Vildagliptin	bd	50	1.5–4.5	62	32–270	Inactive metabolites	Urine ~80%[d]
Saxagliptin	od	5	2–7[e]	50	77–390	Active metabolites	Urine ~60%[d]
Linagliptin	od	5	10–40	1	>10 000	Mostly unchanged	Bile ~80%
Alogliptin	od	25	12–21	24	>14 000	Mostly unchanged	Urine >70%

[a] od, once daily; bd, twice daily.
[b] Concentration causing 50% inhibition of DPP-4 activity.
[c] Fold selectivity for inhibition of DPP-4 versus inhibition of DPP-8 and DPP-9.
[d] Unchanged drug.
[e] Includes metabolites.

(sitagliptin, linagliptin, and alogliptin) interactions. DPP-4 inhibitors are absorbed rapidly, with onset of activity in <10 minutes of administration and t_{max} achieved mostly within 2 hours. They produce >90% inhibition of DPP-4 activity for most of a 24-hour period, although the shorter elimination half-life of vildagliptin requires twice-daily administration compared with once daily for other agents in the class. Two DPP-4 inhibitors are substantially metabolized (vildagliptin to inactive metabolites and saxagliptin to active metabolites), whereas the others undergo little metabolism. Linagliptin is eliminated mostly via the bile into the faeces and can be used without dose adjustment in people with moderate to severe renal impairment. Other members of the class are eliminated in the urine, necessitating dose reduction in people with moderate renal impairment (typically an eGFR <50 ml/min) [60, 60].

Indications and contraindications

DPP-4 inhibitors can be used as monotherapy in people whose type 2 diabetes has responded inadequately to lifestyle measures, and as add-on therapy when metformin or a thiazolidinedione alone has not brought the glucose levels into the target range. DPP-4 inhibitors could be used with other classes of oral agent or insulin, as their mode of action on the β cell is different from that of sulfonylureas and meglitinides, and their ability to reduce glucagon levels might be useful as add-on therapy to insulin even without β-cell function. In practice, however, full efficacy in type 2 diabetes requires adequate β-cell reserve, and there is usually little additional efficacy if a DPP-4 inhibitor is added to a GLP-1 receptor agonist. Lack of weight gain makes DPP-4 inhibitors suitable for individuals with overweight or obesity, and the low risk of hypoglycaemia when used as monotherapy (and

when used with non-insulin-releasing agents) favours their use in people who have only slightly raised basal glycaemia, are close to glycaemic target, or have unpredictable meal times [60,61].

Efficacy

The anti-hyperglycaemic effect of DPP-4 inhibitors is quickly generated, with HbA_{1c} values are typically reduced by ~0.7–1.0% (8–11 mmol/mol). Post-prandial glucose excursions are reduced by ~3 mmol/l and basal glycaemia by ~1–1.5 mmol/l. The glucose-dependent mode of action (i.e. DPP-4 inhibitors only potentiate insulin secretion when glucose concentrations are raised) reduces the risk of any significant hypoglycaemia, lowering concern over missed meals. Thus, there is no dose titration, but it is recommended that fasting and post-prandial glycaemia are reviewed after about two weeks of therapy, especially when added as a second agent. The incretin-raising effects of DPP-4 inhibitors do not appear to be sufficient to reduce gastric emptying or produce a measurable satiety effect. Accordingly, DPP-4 inhibitors do not cause weight gain and may assist with slight weight loss [61–63].

Adverse effects

Substantial clinical experience with DPP-4 inhibitors has indicated a good safety profile to date. In clinical trials (typically 6–12 months), measures of tolerability and adverse events were generally similar to those with placebo or comparator. Owing to their glucose-dependent action on the pancreas, DPP-4 inhibitors carry a low risk of serious hypoglycaemia unless administered along with an agent that itself carries significant risk of hypoglycaemia. Thus, when a DPP-4 inhibitor is used in combination with a sulfonylurea or with insulin, it may be appropriate initially to lower the dose of the sulfonylurea or insulin, especially for those who are only modestly hyperglycaemic and more vulnerable to hypoglycaemia. DPP-4 inhibition has been associated with some hyperplasia of the exocrine pancreas, and there is evidence from several prospective and retrospective clinical studies that DPP-4 inhibition can increase the risk of acute pancreatitis in type 2 diabetes. Although this has not been consistently observed, or numerical data have not been statistically significant, appropriate caution is recommended and a DPP-4 inhibitor should be stopped if pancreatitis is suspected, and alternative therapy sought for people with a history of pancreatitis. Long-term cardiovascular safety studies have raised the possibility of an increased risk of angina during use of some DPP-4 inhibitors, but the evidence is equivocal, and there is lingering concern from these studies that saxagliptin and possibly alogliptin could carry a small increased risk of heart failure [62–64].

In addition to GLP-1 and GIP, there are many natural substrates for DPP-4, including bradykinin, enkephalins, neuropeptide Y, peptide YY1–36, gastrin-releasing polypeptide, substance P, insulin-like growth factor I, the α chains of thyrotropin, luteinizing hormone, and chorionic gonadotropin, and several chemokines such as monocyte chemotactic protein 1 (MCP-1). Hence DPP-4 inhibitors have the potential to influence the hunger–satiety system, gastrointestinal motility, growth, vascular reactivity, and immune mechanisms, but there is little evidence of any clinically significant changes in these physiological processes [61,63]. DPP-4 is also the CD26 T-cell activation antigen, but neither CD26 knockout mice nor the DPP-4-specific inhibitors used in animals or humans have shown any significant untoward immune-related effects. The importance of selective DPP-4 inhibition is also noted because inhibition of related enzymes such as DPP-8 and DPP-9 has produced blood dyscrasias and skin lesions in some species, although not in clinical use. No significant drug interactions have been noted with DPP-4 inhibitors, but evidence of reproductive toxicity in animals warrants discontinuation in pregnancy.

Sodium–glucose cotransporter-2 inhibitors

SGLT-2 is highly expressed in the first segment of the proximal tubules of the kidneys, where it is responsible for the reabsorption of ~90% of glucose in the glomerular filtrate. Partial inhibition of SGLT-2 provides a non-insulin-dependent mechanism to reduce glucose reabsorption, eliminate excess glucose in the urine, and so reduce hyperglycaemia [65]. Studies in the 1980s showed that phlorizin, a naturally occurring inhibitor of sodium–glucose transporters found in apple tree bark, could reduce hyperglycaemia in partially pancreatectomized rodents with diabetes. Phlorizin was degraded too rapidly in the intestine to be used therapeutically, but chemical modifications to minimize intestinal breakdown and increase selectivity against SGLT-2 have given rise to a class of selective SGLT-2 inhibitors represented by canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin (Figure 35.14).

Mode of action

SGLT-2 is a high-capacity secondary active cotransporter that transfers one sodium ion with one glucose molecule down an electrochemical gradient for sodium, generated by, for example, the activity of an $Na^+ - K^+$ ATPase pump [65,66]. SGLT-2 inhibitors interact with SGLT-2 transporters located at the luminal surface of the epithelium lining the initial region of the renal proximal tubules (Figure 35.15). They competitively inhibit the transporter, reducing glucose reabsorption and thereby lowering the renal threshold for glucosuria. In this way, SGLT-2 inhibitors enable ~20–30% of filtered glucose (about 50–100 g glucose/d) to be eliminated in the urine of people with type 2 diabetes [66,68,69]. As the blood glucose concentration declines, both the amount of filtered glucose and the glucosuria decline, minimizing the effect of SGLT-2 inhibition in the euglycaemic range and avoiding frank hypoglycaemia. Because the mechanism is independent of insulin, it will continue to operate under conditions of insulin resistance and β-cell failure, but requires adequate kidney function to filter sufficient glucose for partial SGLT-2 inhibition to create enough glucosuria to impact the hyperglycaemia. The glucosuria induced by SGLT-2 inhibition can assist weight loss and generate a mild osmotic diuresis that may contribute to a small reduction in blood pressure [5,70–73].

SGLT-2 inhibitors can weakly suppress the activity of SGLT-1 transporters (transfer two sodium ions with one glucose or galactose). SGLT-1 is abundant in the intestine and accounts for the absorption of glucose; it is also expressed in the third (straight descending) segment of the proximal tubules, where it is responsible for ~10% of glucose reabsorption. Canagliflozin may interact with SGLT-1 to defer intestinal glucose absorption slightly more distally along the intestinal tract, but it is uncertain whether the concentration of the drug in the renal tubule is sufficient to exert any meaningful inhibition SGLT-1 activity in the kidney [70]. Sotagliflozin is a stronger inhibitor of SGLT-1 and also inhibits SGLT-2; at the time of writing studies in individuals with type 2 diabetes are ongoing.

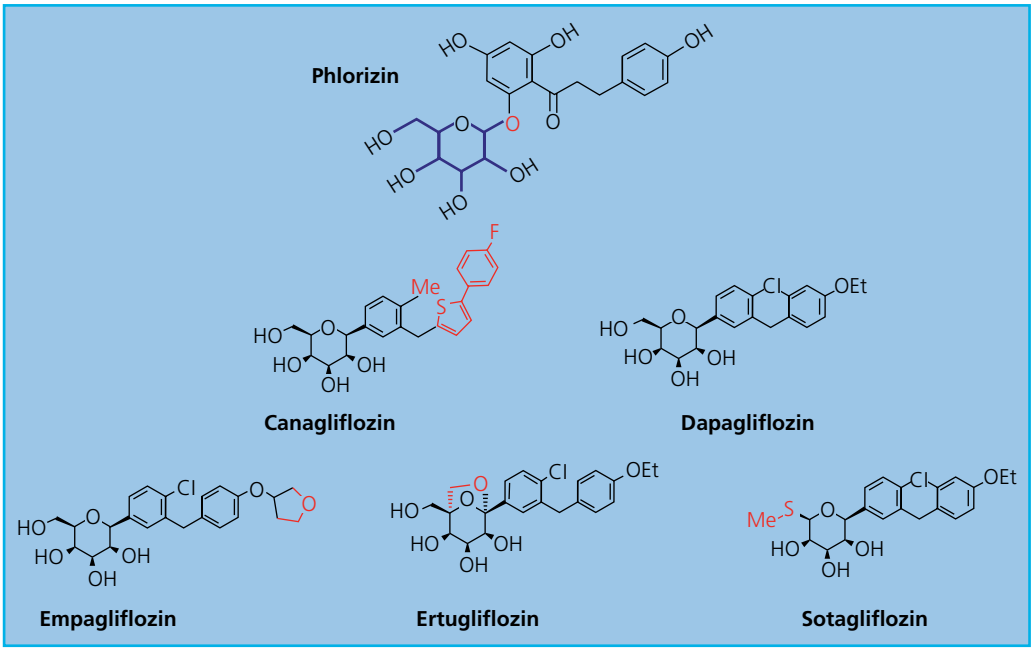

Figure 35.14 Structures of sodium–glucose cotransporter (SGLT) inhibitors. Phlorizin is a naturally occurring inhibitor of SGLT-1 and SGLT-2. Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are selective inhibitors of SGLT-2, and sotagliflozin is an inhibitor of SGLT-1 and SGLT-2.

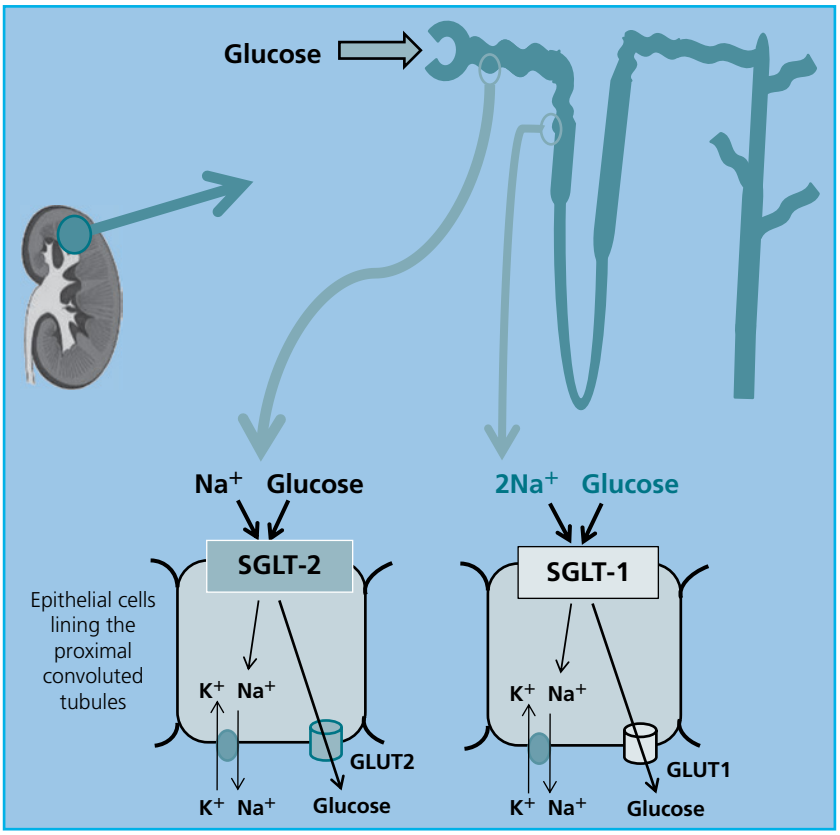

Figure 35.15 Renal sodium–glucose cotransporters (SGLT) reabsorb glucose from the renal proximal tubules. Glucose is filtered at the glomerulus into the proximal tubule and mostly reabsorbed from the initial region of the proximal tubule via the high-capacity transporter SGLT-2. Remaining glucose is reabsorbed more distally along the proximal tubule via the low-capacity transporter SGLT-1. Source: Bailey 2015 [67]. Reproduced by permission.

Table 35.13 Sodium–glucose cotransporter-2 (SGLT-2) inhibitors: dapagliflozin, canagliflozin, empagliflozin, and ertugliflozin.

Agent	Dose (mg/d)	IC_{50}SGLT2 vs SGLT1 (nM)	t_{max} (h)	C_{max}	$t_{1/2}$ (h)
Dapagliflozin	5–10	1.1 vs 1390	1–2	~160 µg/l	~13
Canagliflozin	100–300	2.2 vs 910	1–2	~1–5 mg/l	~13
Empagliflozin	10–25	3.1 vs 8300	~1.5	~250–700 nmol/l	~13
Ertugliflozin	5–15	0.9 vs 1960	~1	~260 µg/l	~17

Pharmacokinetics

The pharmacokinetic properties of SGLT-2 inhibitors are summarized in Table 35.13. They reversibly inhibit SGLT-2 at low nmol/l concentrations by blocking the glucose site for several minutes. SGLT-2 inhibitors are taken as once-daily tablets; they are rapidly absorbed with high bioavailability. In plasma they are mostly protein bound and are degraded mainly through glucuronidation by uridine diphosphoglucuronosyltransferases to inactive metabolites. They show little or no inhibition by or induction of P450 isoforms that metabolize other common medications, and no clinically significant drug interactions have been noted [74].

Indications and contraindications

SGLT-2 inhibitors can be used as monotherapy in people whose type 2 diabetes has not responded adequately to lifestyle measures, although they are more often used as add-on therapy in those whose diabetes is inadequately managed by metformin or another glucose-lowering agent. In principle, an SGLT-2 inhibitor can be used with any other class of oral agent or insulin, as the mode of action is different from those of all other classes of glucose-lowering agents. Body weight reduction makes an SGLT-2 inhibitor suitable for individuals with overweight or obesity, and the low risk of hypoglycaemia renders this class of agent suitable for people with glucose values close to target. Modest reductions of blood pressure in individuals with hypertension can also be expected [71].

Adequate renal function is an important consideration for use of an SGLT-2 inhibitor to enable glucosuric efficacy. Recommendations vary between countries, but an SGLT-2 inhibitor can be used at full daily dosage for eGFR >60 ml/min/1.73 m^2. Although SGLT-2 inhibitors have evident reno-protective effects in clinical trials, current product labels suggest a reduced dose for people with an eGFR value persistently <45 ml/min/1.73 m^2 [75]. Treated individuals with diabetes should be informed about the need to remain hydrated and the risk of initial nocturia and mycotic genital infections. People with insulin-treated type 2 diabetes should ensure that they maintain an adequate insulin dose, since insulin is required for many more physiological purposes than glucose regulation. At the time of writing, some SGLT-2 inhibitors are approved for use as adjunctive therapy with insulin in type 1 diabetes mellitus; again, the importance of maintaining adequate insulin is emphasized to avoid diabetic ketoacidosis. SGLT-2 inhibitors should be discontinued in pregnancy.

Efficacy

The glucose-lowering efficacy of SGLT-2 inhibitors in type 2 diabetes has been confirmed in prospective randomized clinical trials during use as monotherapy and in combination with other glucose-lowering therapies including insulin [71–73]. There is a rapid onset of action to reduce post-prandial and basal hyperglycaemia. HbA_{1c} is typically reduced by ~0.6–1.2% (7–13 mmol/mol), although larger reductions may be seen in people with severe hyperglycaemia and those with good renal function [76]. Efficacy during trials has extended over several years and risk of hypoglycaemia has been low unless SGLT-2 inhibitors are used in combination with an agent that can itself cause hypoglycaemia (such as a sulfonylurea or insulin). Most people achieve a weight loss of ~2–4 kg, which typically levels out by 6–12 months, possibly reflecting an increase in metabolic efficiency or some increase in food intake as the glucose level declines. The weight loss is predominantly a decrease in fat mass, notably from the visceral adipose depot. In clinical trials involving participants with insulin-treated type 2 diabetes, glycaemic indices are often improved while the insulin dose is slightly lowered, and the improvement is maintained over time without insulin dose escalation. Combination of an SGLT-2 inhibitor with insulin can also reduce the weight gain normally associated with insulin therapy.

Randomized controlled cardiovascular outcome trials in individuals with type 2 diabetes have consistently confirmed that SGLT-2 inhibitors reduce systolic and diastolic blood pressure by about 3–5 and 2–3 mmHg, respectively, without dipping into hypotension. These trials have also noted that use of SGLT-2 inhibitors is associated with a reduced occurrence of new-onset heart failure and less worsening of established heart failure, with about 30% fewer hospitalizations for heart failure, mainly among individuals with reduced ejection fraction [77,78]. Fewer cardiovascular deaths have also been recorded with use of SGLT-2 inhibitors in some trials, but this has not been a consistent finding. The reductions in blood pressure and risk of heart failure appear to be independent of the glucose-lowering and weight-lowering effects of SGLT2 inhibitors; indeed, similar reductions in blood pressure and heart failure have been noted in people without diabetes [79]. The cardiovascular effects of SGLT-2 inhibitors are also independent of age, prior history of cardiovascular disease, or treatments for hypertension and heart failure, and occur irrespective of normal or impaired renal function.

Several possible mechanisms appear to contribute to these potentially cardioprotective effects of SGLT-2 inhibitors. Lower blood pressure may initially result in part from the osmotic diuresis and reduction in plasma volume, and be assisted in the longer term by reductions in body weight, glucotoxicity, insulin resistance, and uric acid. The myocardium could also benefit from reduced plasma volume, reduced vascular resistance, and increased availability of ketones as an energy source from whole-body fatty acid metabolism. Additionally, SGLT-2 inhibitors have been reported to improve myocardial energetics by increasing myocardial catabolism of branched-chain amino acids and inhibiting the Na^+/H^+ exchanger [80].

SGLT-2 inhibitors often cause an initial temporary drop in eGFR by ~5 ml/min/1.73 m^2, which usually recovers by 3–6 months. Thereafter, use of an SGLT-2 inhibitor slows the long-term decline in eGFR, accompanied by reductions in the onset and progression of micro- and macroalbuminuria. These effects, which preserve

renal function, are independent of the glucose-lowering and weight-lowering effects of SGLT-2 inhibitors and are also evident in people without diabetes. The effects are also independent of age, baseline eGFR, prior or existing cardiovascular disease, or antihypertensive therapies. One postulated mechanism is the effect of SGLT-2 inhibition to increase sodium retention within the lumen of the nephron. The raised luminal sodium concentration carries through to the ascending limb of the loop of Henle, where it is sensed by the macula densa. This increases the tubulo-glomerular feedback of adenosine to constrict the afferent glomerular arterioles, which reduces intra-glomerular pressure [81]. Additional potential reno-protective effects of SGLT-2 inhibitors may include localized reductions of oxidative stress and inflammation within the kidney.

Adverse effects

The glucosuric effect of SGLT-2 inhibitors increases the risk of genital infections, particularly vulvovaginal mycotic infections in women during the initial months of therapy, and there has also been a small increase in the risk of urinary tract infections in some studies. The occurrence and severity of these infections can be reduced by appropriate advice when starting therapy and most of these infections respond to standard treatments, often by self-management. The osmotic diuresis generated by the glucosuria (usually <500 ml/d) requires patient attention to adequate hydration, especially in hot climates, and should be emphasized when initiating therapy. Because the eGFR may temporarily decline after introduction of an SGLT-2 inhibitor, extra caution is recommended for people receiving diuretic therapy, although electrolyte imbalances have not been seen in clinical trials [75].

Accounts of atypical ketoacidosis in individuals treated with an SGLT-2 inhibitor have described a hyperosmolar ketoacidosis with only modest hyperglycaemia. Many of these people had type 1 diabetes or were insulin-treated individuals of unclear diagnosis in whom the insulin dose had been over-reduced because the hyperglycaemia was reduced by the SGLT-2 inhibitor. Basal insulin should be maintained in insulinopenic individuals, as this reduces lipolysis (thereby reducing the supply of fatty acids for ketogenesis) and is required for other physiological purposes beyond glycaemic management. SGLT-2 inhibition may also reduce renal clearance of ketones and may cause a compensatory increase in glucagon release, especially at low glucose levels, which can promote ketogenesis [82]. Thus, people with a history of ketotic episodes are unlikely to be appropriate for SGLT-2 inhibitor therapy.

Because SGLT-2 inhibitors do not interfere with P450 isoenzymes, they do not appear to have any clinically meaningful drug interactions. Minor changes in the circulating lipid profile have been reported with SGLT-2 inhibitors, notably some increases in LDL and HDL cholesterol, but without altering the LDL-to-HDL ratio. During clinical trials, the numbers of major adverse cardiovascular events have generally been similar to or fewer than with comparator therapies, leaving uncertainty regarding any significant class effects on atherosclerotic disease.

Oral glucagon-like peptide-1 receptor agonist

As noted in the section on DPP-4 inhibitors and considered in detail in Chapter 36, GLP-1 is an incretin hormone secreted from intestinal L cells during meal digestion. It potentiates nutrient-induced insulin secretion, suppresses excess glucagon secretion, exerts a satiety effect, and delays gastric emptying. Several subcutaneously injected analogues of GLP-1 that mimic the effects of the native hormone are established therapies for type 2 diabetes. Recently introduced (2019) is an oral formulation of the GLP-1 receptor agonist semaglutide [83].

Semaglutide is structurally similar to native GLP-1: it has a substitution of alanine to aminoisobutyric acid at position 8 (N2 of the active peptide) to prevent degradation by DPP-4. There is a C18 fatty di-acid chain attached to the lysine at position 26 to enable binding to albumin to prolong circulation time, and a lysine to arginine substitution at position 34 to ensure fatty acid linkage only at position 26. To facilitate absorption across the gastric epithelium, semaglutide is formulated into a tablet with the absorption enhancer sodium hydroxybenzoylamino-caprylate (SNAC), which protects the peptide from proteolytic degradation by raising the pH around the peptide and assisting transcellular absorption. Oral semaglutide is taken on an empty stomach, usually in the morning, and food is avoided for at least 30 minutes to allow adequate drug absorption.

Oral and injectable formulations of semaglutide are similarly effective in reducing blood glucose (with low risk of hypoglycaemia) and body weight, as considered in detail in Chapter 36. In clinical trials, oral semaglutide has similar beneficial cardio-renal effects, safety profile, and therapeutic applications to injectable semaglutide.

α-Glucosidase inhibitors

Studies conducted in the late 1970s noted that inhibitors of intestinal α-glucosidase enzymes could retard the final steps of carbohydrate digestion, with a consequent delay in the absorption of sugars. By the early 1980s, it was demonstrated that this approach could reduce postprandial hyperglycaemia in diabetes [84]. Acarbose, the first α-glucosidase inhibitor, was introduced in the early 1990s. Subsequently, two further agents, miglitol and voglibose, were introduced in some countries (Figure 35.16). In people who consume meals containing complex carbohydrate, α-glucosidase inhibitors can effectively reduce post-prandial glucose excursions. These agents also have a good safety record, but their application has been limited by gastrointestinal side effects and modest efficacy.

Mode of action

α-Glucosidase inhibitors competitively inhibit the activity of α-glucosidase enzymes in the brush border of enterocytes lining the intestinal villi (Figure 35.17). They bind to the enzymes with high affinity, preventing the enzymes from cleaving disaccharides and oligosaccharides into monosaccharides. This delays completion of carbohydrate digestion and can defer the process distally along the intestinal tract, leading to a delay in glucose absorption [84,85]. Different α-glucosidase inhibitors have different affinities for the various α-glucosidase enzymes. This gives slightly different activity profiles (e.g. acarbose has greatest affinity for glycoamylase > sucrase > maltase > dextrinases, whereas miglitol is a stronger inhibitor of sucrase).

It is emphasized that α-glucosidase inhibitors can only be effective if the person is consuming complex digestible carbohydrate. These agents do not significantly affect the absorption of glucose *per se*. By moving glucose absorption more distally along the intestinal tract, α-glucosidase inhibitors may alter the release of

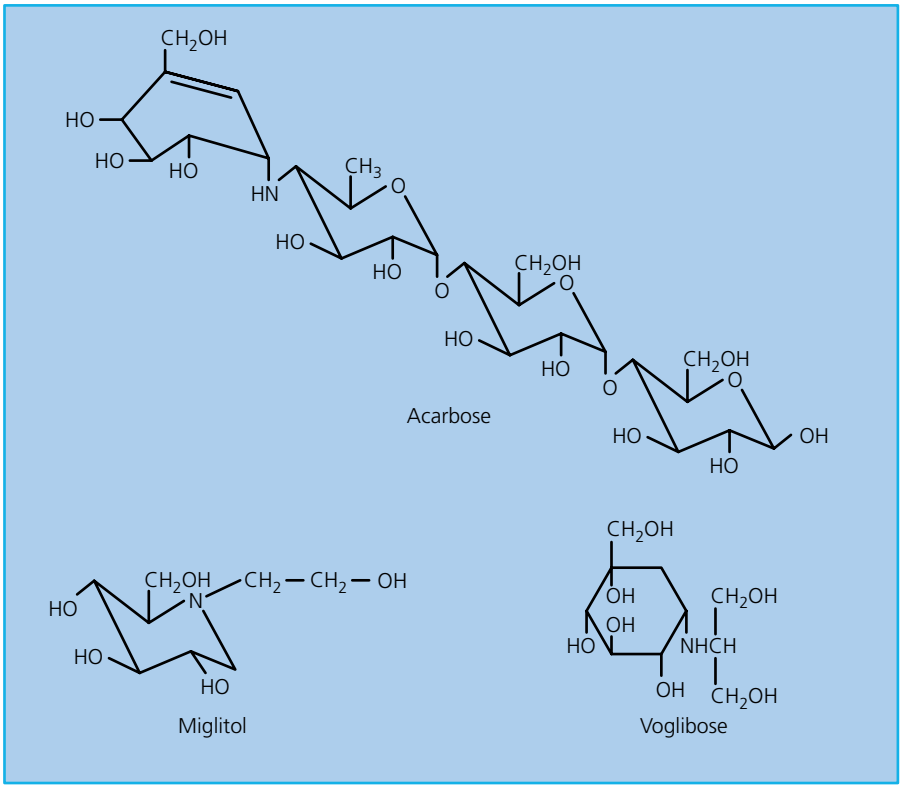

Figure 35.16 Chemical structures of the α-glucosidase inhibitors acarbose, miglitol, and voglibose.

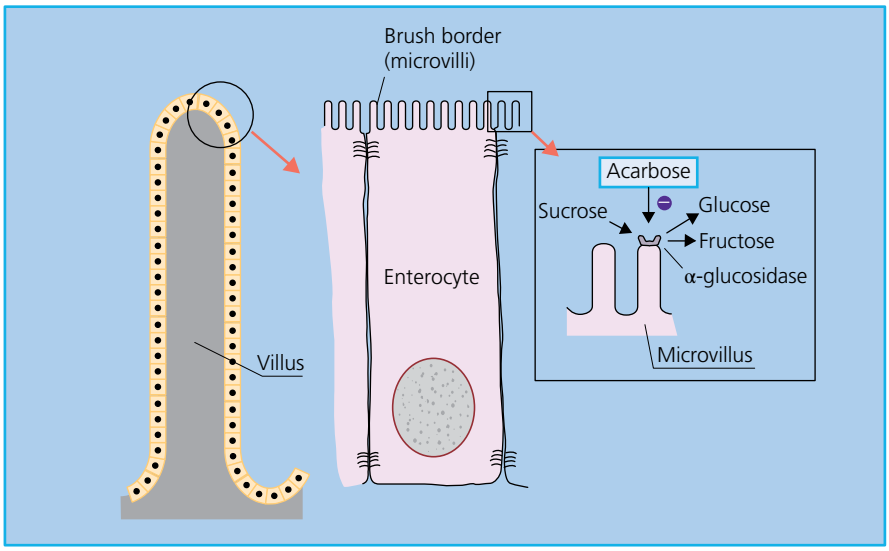

Figure 35.17 Mode of action of α-glucosidase inhibitors. α-Glucosidase inhibitors competitively inhibit the activity of α-glucosidase enzymes in the brush border of enterocytes lining the intestinal villi, preventing these enzymes from cleaving disaccharides and oligosaccharides into monosaccharides. This delays carbohydrate digestion.

glucose-dependent incretin hormones such as GIP and GLP-1, which affect nutrient-induced insulin secretion. Hence release of GIP, which occurs mainly from the jejunal mucosa, may be reduced by α-glucosidase inhibitors, whereas secretion of GLP-1 (mostly from the ileal mucosa) is increased. α-Glucosidase inhibitors probably reduce post-prandial insulin concentrations through the attenuated rise in post-prandial glucose levels [84, 85].

Pharmacokinetics

Acarbose is degraded by amylases in the small intestine and by intestinal bacteria; <2% of the unchanged drug is absorbed along with some of the intestinal degradation products. Absorbed material is mostly eliminated in the urine within 24 hours [84]. Miglitol is almost completely absorbed and eliminated unchanged in the urine.

Indications and contraindications

α-Glucosidase inhibitors can be used as monotherapy, usually for people with type 2 diabetes with post-prandial hyperglycaemia but only slightly raised fasting glycaemia; however, they are more commonly used as an add-on to other therapies, again to target post-prandial hyperglycaemia [84, 85]. α-Glucosidase inhibitors can also

be used to extend the post-prandial period to reduce inter-prandial glycaemic troughs or hypoglycaemia in individuals receiving a sulfonylurea and/or insulin. Acarbose prevents the progression of IGT to type 2 diabetes [86], although this is not a licensed use.

When starting an α-glucosidase inhibitor, advice should be given that a diet containing complex digestible carbohydrate is important. α-Glucosidase inhibitors should be taken with meals, starting with a low dose (e.g. 50 mg/day acarbose) and slowly uptitrating over several weeks. Monitoring of post-prandial glycaemia is often helpful. Hypoglycaemia is unlikely when used as monotherapy, but gastrointestinal symptoms commonly limit initial tolerability and dose titration. Symptoms tend to be reduced by slow titration and usually subside with time, possibly reflecting some adaptation of the intestinal tract, but tolerability is poor.

α-Glucosidase inhibitors are contraindicated for people with a history of chronic intestinal disease, and as high dosages of acarbose can occasionally increase liver enzyme concentrations, it is recommended to measure transaminase concentrations periodically in those receiving a maximum dosage (200 mg acarbose three times daily). Raised liver enzymes should remit as the dosage is reduced, otherwise alternative causes of hepatic dysfunction should be considered.

Efficacy

Because α-glucosidase inhibitors target post-prandial glucose excursions during meals that contain complex carbohydrate, their effectiveness is entirely dependent on following an appropriate diet. As monotherapy, these agents can reduce peak post-prandial glucose concentrations by 1–4 mmol/l. The incremental area under the post-prandial plasma glucose curve can be more than halved in some individuals, and there is usually some extended duration of effect to modestly lower basal glycaemia up to ~1 mmol/l. The decrease in HbA_{1c} can be 0.5–1.0% (6–11 mmol/mol), provided that a high dose of the drug is tolerated and an appropriate diet is maintained [84, 85].

Although overall reductions in HbA_{1c} are usually modest, α-glucosidase inhibitors offer several useful features: they do not cause weight gain or frank hypoglycaemia and they may reduce inter-prandial episodes of hypoglycaemia. When combined with other anti-diabetes agents, α-glucosidase inhibitors can reduce post-prandial hyperinsulinaemia, and they often lower plasma triglyceride concentrations. An α-glucosidase inhibitor can produce minor alterations to the intestinal absorption of other oral glucose-lowering agents when used in combination therapy, but α-glucosidase inhibitors usually provide additive efficacy gains when used in combination with any other class of glucose-lowering agent [84, 85]. Despite the link between post-prandial hyperglycaemia and cardiovascular risk, a five-year study in people with coronary heart disease and IGT found no effect of acarbose on a composite of major adverse cardiovascular events (cardiovascular death, non-fatal MI or stroke, unstable angina, or hospitalization for heart failure) [87].

Adverse effects

Gastrointestinal side effects represent the main problem with α-glucosidase inhibitors. For example, in the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial, 31% of acarbose-treated participants compared with 19% on placebo discontinued treatment early [88]. If the dosage is too high (relative to the amount of complex carbohydrate in the meal), undigested oligosaccharides pass into the large bowel. These are fermented, causing flatulence, abdominal discomfort, and sometimes diarrhoea, but usually ameliorating with slower titration and time. Hypoglycaemia is uncommon and there are no clinically significant drug interactions, although use in conjunction with agents affecting gut motility or cholestyramine is not recommended.

Bromocriptine

The dopamine D2 receptor agonist bromocriptine (Figure 35.18), which has long been used to treat pituitary tumours and Parkinson disease (albeit in a different formulation), has an indication for use in the treatment of type 2 diabetes in some countries [89, 90].

Mode of action

Studies in animals have noted that the interruption of dopaminergic pathways in the hypothalamus is associated with the development of insulin resistance, and this can be reversed by localized dopamine infusion. Studies in individuals with type 2 diabetes suggest that a low dose of a rapid-acting formulation of bromocriptine administered early in the morning soon after waking can temporarily boost hypothalamic dopamine. This appears to rebalance several features of the circadian periodicity of glucose homeostasis by reducing sympathetic tone and enhancing the neural suppression of hepatic glucose production. Additionally, there is a reduction of adipose tissue lipolysis and an improvement in peripheral glucose disposal without elevation of plasma insulin, indicating improved peripheral insulin sensitivity [89, 90].

Pharmacokinetics

The low-dose quick-release formulation of bromocriptine used for blood glucose lowering is rapidly absorbed (t_{max} by 1 hour), highly protein bound, rapidly removed by the liver (mostly metabolized by CYP3A4), and eliminated via the bile; the half-life is ~6 hours. Prolactin levels are reduced consistent with increased dopaminergic activity.

Indications and contraindications

Based on considerable experience with the use of bromocriptine for other purposes, use to treat type 2 diabetes requires caution if individuals are prone to low blood pressure, various psychotic disorders, or somnolence, and exclusion of those who experience migraine or take dopaminergic antagonists. Potential interactions with other medications that influence or may be influenced by changes in CYP3A4 should be appreciated, and evidence regarding use during pregnancy is limited.

Efficacy

In clinical trials, participants with type 2 diabetes receiving a low dose (0.8–4.8 mg) of quickly acting bromocriptine early in the morning showed HbA_{1c} reductions of ~0.5–0.7% (5–8 mmol/mol) when it

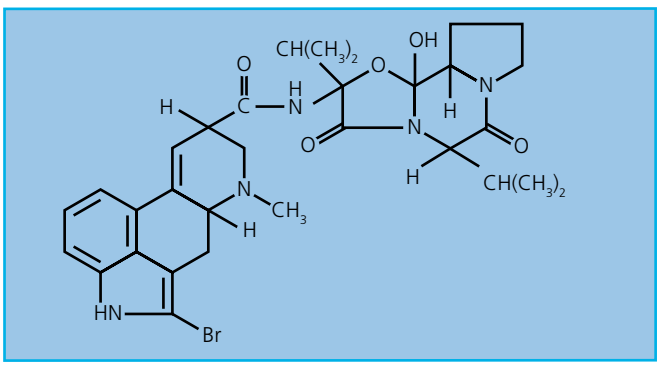

Figure 35.18 Chemical structure of bromocriptine.

was taken as monotherapy or in combination with other oral glucose-lowering agents. Fasting and post-prandial glucose, fatty acid, and triglyceride concentrations were reduced, insulin was not raised, risk of hypoglycaemia was low, and there was no weight gain [89,90].

Adverse effects

Although high doses of bromocriptine carry some long-term risk for pulmonary and pericardial fibrosis, hypotension, and aggravation of psychotic disorders, these were not seen with low doses during clinical trials for type 2 diabetes.

Colesevelam

In addition to its use as a bile acid sequestrant, colesevelam (a polyallylamine derivative) also has an indication for glucose lowering in some countries.

Mode of action

The glucose-lowering mechanism of colesevelam is not clear. By interrupting the enterohepatic circulation of bile acids, colesevelam appears to reduce the availability of bile acids to activate the bile acid receptor-1 (TGR5) and the farnesoid X receptor (FXR), which results in increased hepatic glucose metabolism [91]. A further possibility is that the bile acids are carried more distally along the intestine owing to their entrapment by colesevelam. This could bring more bile acids into contact with TGR5 receptors on L cells, which could enhance the secretion of GLP-1.

Pharmacokinetics

Up to three 625 mg tablets of colesevelam can be taken with each of two main meals daily; the colesevelam is not absorbed.

Indications and contraindications

Colesevelam requires caution if any intestinal disorders, especially obstruction, are known or suspected. Colesevelam can alter the absorption of other oral medications, including oral glucose-lowering therapies, and dose adjustments may be required.

Efficacy

Clinical trials with colesevelam in type 2 diabetes have noted modest reductions of HbA_{1c} of ~0.5% (5 mmol/mol) when used as an add-on to metformin, sulfonylurea, or insulin. There is no effect on body weight, low risk of hypoglycaemia, and, consistent with its use in the treatment of hypercholesterolemia, there is usually a reduction in LDL cholesterol [91].

Adverse effects

Colesevelam may increase circulating triglycerides and cause abdominal symptoms, especially constipation.

Anti-obesity therapies

Obesity, especially excess visceral adiposity, predisposes to diabetes, increases insulin resistance, complicates glycaemic management, and substantially increases the risk of vascular disease [92]. The blood glucose–lowering efficacy of lifestyle measures to reduce adiposity in individuals with type 2 diabetes and obesity is well appreciated, although it is often difficult to achieve and maintain significant weight loss in these people [93]. Several studies have noted the reductions in blood glucose that accompany the use of pharmacological anti-obesity therapies in type 2 diabetes. Whether this is entirely explained by greater weight loss and improved diet is unclear, because some anti-obesity therapies may have some modest independent glucose-lowering effects [94].

In conjunction with a mildly hypocaloric and reduced-fat diet, the intestinal lipase inhibitor orlistat (120 mg three times daily with meals) can reduce dietary fat absorption by up to 30%. In individuals with type 2 diabetes and overweight or obesity, this typically reduces weight by an extra 2–3 kg, and additional reductions in HbA_{1c} of 0.28–1.1% (3–12 mmol/mol) have been reported [94].

Other anti-obesity agents, notably a phentermine–topiramate combination (Qsymia®, Vivus, Campbell, CA, USA), and a bupropion–naltrexone combination (Contrave®, Currax Pharmaceuticals, Brentwood, TN, USA), have been shown in clinical trials to improve glycaemic indices in people with type 2 diabetes in association with weight loss [94]. However, these anti-obesity therapies are not approved in many regions; carry their own contraindications, cautions, and side effects; and may interfere with the absorption or actions of other therapies, including glucose-lowering agents. The use of high doses of some GLP-1 receptor agonists to address obesity as well as type 2 diabetes is considered in Chapters 36 and 38.

Fixed-dose combinations

As early, individualized, and intensified interventional approaches to manage hyperglycaemia in type 2 diabetes have gained acceptance, the use of combinations of two or more oral agents with different mechanisms of action has become commonplace [3,4]. Indeed, some guidelines suggest that individuals presenting with moderate to severe hyperglycaemia may be considered for initial pharmacotherapy with a combination of glucose-lowering agents [4]. To facilitate combination therapy, several fixed-dose, single-tablet dual combinations are available (Table 35.14). These are designed to provide bioequivalence and thereby similar efficacy, although minor adjustments to the formulation may also allow some extra blood glucose–lowering efficacy.

Fixed-dose dual combinations can offer convenience, reduce the *pill burden*, and simplify administration regimens, and they may increase medication taking compared with equivalent combinations of separate tablets. Lower doses of two different types of agents rather than a high dose of one agent may also provide a way to achieve efficacy while circumventing adverse effects [95]. Although single tablets could reduce titration flexibility, most of the commonly used dosage combinations have been accommodated. A recent study has demonstrated rapid and sustained improvements in glucose levels with initial triple therapy [96], and fixed-dose triple combination tablets (e.g. metformin/linagliptin/empagliflozin and metformin/saxagliptin/dapagliflozin) are now becoming available [97]. It is reiterated that dose-related side effects of any combination therapy necessitate the same cautions and contraindications as apply to each active component.

Conclusions

A minimalistic archetypal algorithm to treat hyperglycaemia in type 2 diabetes is shown in Figure 35.19. This illustrates the typical sequence of pharmacological interventions advocated in most

Table 35.14 Fixed-dose single-tablet dual combinations of glucose-lowering agents.

Tablet[a]	Components	Strengths (mg)
Glucovance	Metformin + glibenclamide	250 : 1.25; 500 : 2.5; 500 : 5
Metaglip	Metformin + glipizide	250 : 2.5; 500 : 2.5; 500 : 5
Avandamet	Metformin + rosiglitazone	500 : 1; 500 : 4; 500 : 2; 1000 : 2; 1000 : 4
Competact (Actoplus Met)	Metformin + pioglitazone	500 : 15; 850 : 15
Eucreas	Metformin + vildagliptin	850 : 50; 1000 : 50
Janumet	Metformin + sitagliptin	500 : 50; 1000 : 50;
Prandimet	Metformin + repaglinide	500 : 1; 500 : 2
Kombiglyze	Metformin + saxagliptin	500 : 5; 1000 : 2.5; 1000 : 5
Jentadueto	Metformin + linagliptin	500 : 2.5; 850 : 2.5; 1000 : 2.5
Kazano (Vipdomet)	Metformin + alogliptin	500 : 12.5; 1000 : 12.5
Avaglim (Avandaryl)	Rosiglitazone + glimepiride	4:1; 4:2; 4 : 4; 8:2; 8 : 4
Tandemact (Duetact)	Pioglitazone + glimepiride	30 : 2, 30 : 4, 45 : 4
Xigduo	Metformin + dapagliflozin	850 : 5; 1000 : 5
Vokanamet	Metformin + canagliflozin	1000 : 50
Incresync	Pioglitazone + alogliptin	30 : 12.5
Glyxambi	Empagliflozin + linagliptin	10 : 5; 25 : 5
Synjardy	Metformin + empagliflozin	850 : 5; 850 : 12.5; 1000 : 5; 1000 : 12.5
Segluramet	Metformin + ertugliflozin	500/2.5; 500/7.5; 1000/2.5; 1000/7.5

[a] The availability of tablets and component strengths differ between countries. Names vary between Europe and the USA. Alternative names are given in parentheses.

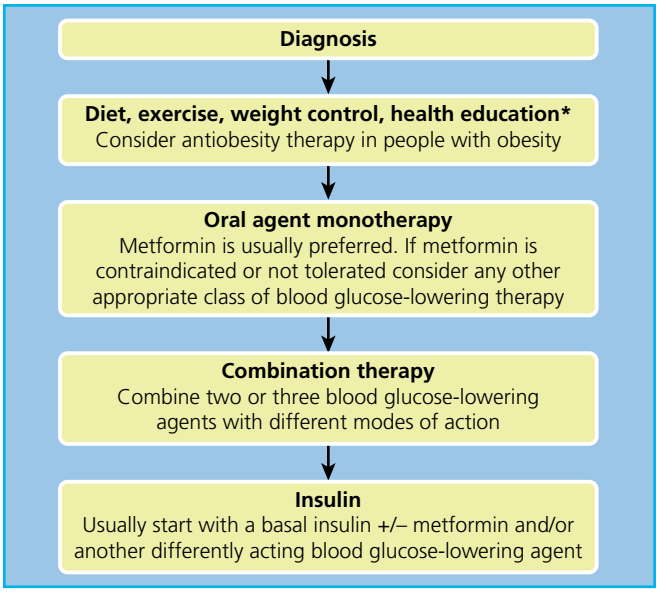

Figure 35.19 Archetypal algorithm used in the treatment of hyperglycaemia in type 2 diabetes (except for those presenting with severe hyperglycaemia who may require immediate insulin therapy). Start with lifestyle measures (diet and exercise). If the individualized glycaemic target is not achieved quickly using lifestyle measures, then add pharmacological therapy without delay. The selected monotherapy is uptitrated to achieve the desired glycaemic effect. If an uptitration step does not add benefit or is not tolerated, go back a step. When the desired glycaemic effect is not achieved or adequate titration is not tolerated, move promptly to the addition of a second agent with a different mode of action and uptitrate. If the desired glycaemic control is not achieved or maintained, consider triple therapy or introduce insulin while maintaining one or two of the existing therapies where appropriate. Respect drug cautions and contraindications at all times, monitor as required, and try to select glycaemic targets that are realistic, safely achievable, and avoid hypoglycaemia. Various guidelines (e.g. see [3, 4]) offer more detail with suggested glycaemic targets and suggested sequence orders for the introduction of the pharmacotherapies. *Lifestyle advice is reinforced throughout.

current guidelines. Guidelines should be interpreted with flexibility, however, to ensure that the care plan, treatment targets, and selection of therapies are individualized to suit the circumstances of the patient. The value of lifestyle intervention as initial and ongoing therapy in conjunction with pharmacological agents should not be underestimated. In view of the progressive natural history of type 2 diabetes, the introduction of drug therapy, the need for periodic uptitration of dosage, and the use of combination therapy can be expected for most people with type 2 diabetes.

A consensus report by the American Diabetes Association and the European Association for the Study of Diabetes suggests that the preferred first-line glucose-lowering agent is usually metformin. If adequate glycaemic levels are not achieved or maintained, the addition of a second pharmacological agent should take particular account of a high level of risk or existence of cardiovascular and/or renal disease irrespective of the extent of hyperglycaemia [3]. Addition of a GLP-1 receptor agonist is favoured if atherosclerotic cardiovascular disease predominates, whereas addition of an SGLT-2 inhibitor is favoured if heart failure or chronic kidney disease predominates. All available glucose-lowering agents could be considered as second-line pharmacotherapy for individuals at lesser risk of cardiovascular or renal complications, taking account of the need to avoid hypoglycaemia, control body weight, and respect affordability.

The latest consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology also gives emphasis to the importance of weight management and addressing key cardiovascular risk factors (blood pressure and lipids) while avoiding hypoglycaemia [4]. Metformin remains the preferred first-line glucose-lowering agent, but this consensus defines HbA_{1c} levels at which dual and triple combination therapy should be considered, whether newly diagnosed or not. Thus, two differently acting glucose-lowering agents are suggested for people with $HbA_{1c} \geq 7.5\%$ (59 mmol/mol) and triple therapy if $HbA_{1c} > 9\%$ (75 mmol/mol), or insulin if significantly symptomatic.

A range of differently acting oral agents is available: metformin and thiazolidinediones counter insulin resistance, but in different ways; sulfonylureas, meglitinides, and DPP-4 inhibitors increase insulin secretion, but with differences of time course and mechanism; SGLT-2 inhibitors increase renal glucose elimination; and α-glucosidase inhibitors slow carbohydrate digestion. Additionally, GLP-1 receptor agonists increase insulin secretion and reduce glucagon. When adequate glycaemic levels are not achieved or not maintained, it is important to proceed to the next therapeutic stage without delay to avoid periods of excessive hyperglycaemia. Insulin should be considered when other therapies do not provide adequate glycaemic levels or are unsuitable. Integrated management to address cardiovascular risk and comorbid conditions is essential. Glucose monitoring, making therapeutic adjustments for efficacy, safety, avoidance of hypoglycaemia, and contraindications, requires constant vigilance and forms an integral part of the treatment process. Early, effective, and sustained glycaemic management is essential to minimize the risk of complications later in life.

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36 Non-insulin Parenteral Therapies

Tina Vilsbøll, Mikkel Christensen, Andreas Andersen, and Filip K. Knop
University of Copenhagen, Copenhagen, Denmark

Key points

- Obtaining sufficient systemic exposure of peptide-based drugs following oral administration is challenging owing to the acidic environment, the presence of proteolytic enzymes in the stomach, and the limited permeability of peptides through the gastrointestinal epithelium.
- Several available non-insulin parenteral therapies used for the treatment of type 2 diabetes are based on the gut-derived hormone glucagon-like peptide 1 (GLP-1).
- GLP-1 is a glucose-lowering (via insulinotropic and glucagonostatic effects) and satiety-promoting hormone secreted from enteroendocrine L cells found in the intestinal epithelium.
- GLP-1 receptor agonists (GLP-1RAs) form part of the treatment algorithms and guidelines for type 2 diabetes.
- GLP-1RAs target a broad spectrum of the pathophysiology of type 2 diabetes, improving glycaemic levels and reducing hunger, food intake, and body weight.
- Differences in the structure, pharmacokinetics, and size of the different GLP-1RAs determine their individual effects on glycated haemoglobin (HbA_{1c}), body weight, dosing frequency (convenience), and tolerability (adverse effects).
- Adverse effects of GLP-1RAs typically affect the gastrointestinal tract (mainly nausea, vomiting, and/or diarrhoea) in a dose-dependent manner and diminish over time.
- Large-scale cardiovascular outcome trials have shown beneficial effects of continuous-acting GLP-1RA treatment added to standard of care, including a reduced risk of major adverse cardiovascular events (non-fatal stroke, non-fatal myocardial infarction, and cardiovascular-related death).
- One available non-insulin parenteral therapy based on the pancreatic β-cell hormone amylin is available as adjunct treatment of insulin-treated type 1 diabetes and type 2 diabetes.
- Amylin is co-secreted with insulin from β cells and reduces gastric emptying, appetite, and post-prandial glucagon secretion.
- Amylin analogues have clinical benefits on HbA_{1c} and body weight in diabetes.
- Non-insulin parenteral therapies based on single-molecule dual- or triple-receptor agonists acting via the GLP-1 receptor, the glucose-dependent insulinotropic polypeptide (GIP) receptor, the amylin receptor, and/or the glucagon receptor are currently being evaluated for the treatment of type 2 diabetes.

During recent decades, the globally increasing prevalence of obesity and associated type 2 diabetes has promoted extensive research with the aim of clarifying the physiological and pharmacological role of pancreas- and gut-derived peptide hormones in the regulation of glucose homeostasis and feeding behaviour. Exploitation of these peptide hormones for the treatment of diabetes has primarily relied on the development of stable peptide-based drugs (suitable for subcutaneous injection, i.e. parenteral therapies) mimicking and potentiating the effects of the endogenous peptide hormones.

Glucagon-like peptide 1, the GLP-1 receptor, and GLP-1 receptor agonists

The successful development of glucose-lowering drugs based on the physiological effects of the gut incretin hormone glucagon-like peptide 1 (GLP-1), a peptide hormone released from enteroendocrine L cells in response to nutrient ingestion and acting through the GLP-1 receptor (GLP-1R), has increased treatment options and helped clinicians tailor individualized treatments for people with type 2 diabetes. GLP-1-based treatment modalities (i.e. the small-molecule dipeptidyl peptidase 4 [DPP-4] inhibitors reducing the enzymatic inactivation and degradation of endogenous GLP-1 and the exogenous peptide-based GLP-1R agonists [GLP-1RAs]) have been welcomed by healthcare professionals and people with diabetes. In particular, the GLP-1RA drug class is a pivotal part of the international type 2 diabetes treatment algorithms and guidelines, because of its glucose-dependent glucose-lowering action (active only when plasma glucose levels are high with a consequent low risk of hypoglycaemia), body weight–reducing effect, and cardiovascular protective effects [1–3]. The GLP-1RA drug class represents one of the most thoroughly investigated and monitored in terms of safety and efficacy owing to the increased requirements of regulatory agencies (particularly the US Food and Drug Administration [FDA] and European Medicines Agency [EMA]) for extensive safety data on new anti-diabetes drugs coinciding with final development of these drugs. A few GLP-1RAs have also been

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approved for the treatment of overweight and obesity and currently several studies are evaluating the applicability of GLP-1RA treatment in other metabolic disease states and related conditions.

In the first part of the chapter, a historical overview of the investigations leading to the discovery of the gut incretin hormone GLP-1 and its potential as a glucose-lowering drug is presented. The physiology of native GLP-1 is outlined, followed by the pharmacology, safety, and efficacy of the individual GLP-1RAs currently available for the treatment of type 2 diabetes. We also include the recently developed, first orally available GLP-1RA, oral semaglutide (Rybelsus®, Novo Nordisk, Bagsværd, Denmark). Finally, perspectives for GLP-1RA treatment within other disease areas and their potential position in future treatment algorithms are highlighted.

Historical overview

The introduction of GLP-1-based treatment modalities at the beginning of the third millennium was the result of a century of investigations. In 1906, extracts of mucosa from porcine small intestine were tested by Moore et al. as a treatment for diabetes in the hope that, 'the pancreas secretion might be stimulated by the substance of the nature of a hormone yielded by the duodenal mucosa membrane' [4]. In 1928, Zunz and LaBarre described a hypoglycaemic effect following injection of extracts from small intestinal mucosa and, using cross-circulation experiments, showed that the effect was mediated through the pancreas [5]. Four years later, LaBarre named the unidentified substance thought to exert this effect *incretin* in order to dissociate it from secretin (which stimulates exocrine pancreatic secretion), discovered by Bayliss and Starling at the beginning of the twentieth century [6]. Then, in 1964, McIntyre et al. and Elrick et al. demonstrated that orally administered glucose evokes a greater insulin response than intravenously administered glucose, and both groups hypothesized that gut-derived factors could have potentiating effects on insulin secretion after oral glucose ingestion [7,8]. A few years later, in 1967, this finding was confirmed by Perley and Kipnis, who administered oral glucose and, on a separate day, copied the oral glucose curve with an isoglycaemic intravenous glucose infusion in individuals of normal weight and with obesity with diabetes, and in healthy individuals without diabetes [9]. They concluded that the insulin response to isoglycaemic intravenous glucose administration only amounted to 30–40% of that seen after oral administration of glucose; they had come across *the incretin effect*, the phenomenon of oral glucose eliciting a higher insulin response than intravenous glucose at identical plasma glucose profiles. However, at that time the insulinotropic substances eliciting this effect were unknown.

In 1970, gastric inhibitory polypeptide, secreted from small intestinal enteroendocrine K cells in response to ingestion of nutrients, was discovered [10] and, eventually, this 42 amino acid polypeptide was shown to be insulinotropic at elevated glucose concentrations and was renamed glucose-dependent insulinotropic polypeptide (GIP) [11]. Later, experimental and clinical studies suggested that the gut produces more than a single insulinotropic hormone of importance for glucose homeostasis [12]. In 1983, the gene encoding the human pancreatic hormone, glucagon, was cloned, and the structure of its precursor, proglucagon, was surprisingly shown to include the sequence of two glucagon-like peptides including GLP-1 (Figure 36.1) in addition to glucagon itself [13]. The gene was found to be expressed in both pancreatic α cells and enteroendocrine L cells in the small intestine [14]. The primary transcripts and translational products of the gene in the two types of cells are identical, but the post-translational processing differs in the two tissues (Figure 36.2) [14–16]. In the pancreas, proglucagon is cleaved by prohormone convertase 2 to glucagon, glicentin-related pancreatic peptide (GRPP), and a major proglucagon fragment. Apart from glucagon, these fragments seem to be biologically inactive. In contrast, in the intestinal L cells, proglucagon is processed by prohormone convertase 1/3 to GLP-1, glucagon-like peptide 2 (GLP-2), and glicentin. The 30 amino acid peptide GLP-1 is secreted in response to nutrient ingestion and is strongly insulinotropic, an incretin hormone [17,18]. GLP-2 is also secreted in response to nutrient ingestion and is a key regulator of small intestinal growth; GLP-2 receptor agonists have been developed for the treatment of short bowel syndrome [19,20]. The bioactive forms of GLP-1, amidated and glycine-extended GLP-1, respectively, are designated GLP-1(7–36) amide and GLP-1(7–37) (Figure 36.1).

Many hormones have been suspected to contribute to the incretin effect, but today there is ample evidence to suggest that the incretin effect is mainly conveyed by the two incretin hormones, GIP and GLP-1. In 1983, Nauck et al. showed that the incretin effect is reduced in people with type 2 diabetes [21]. The

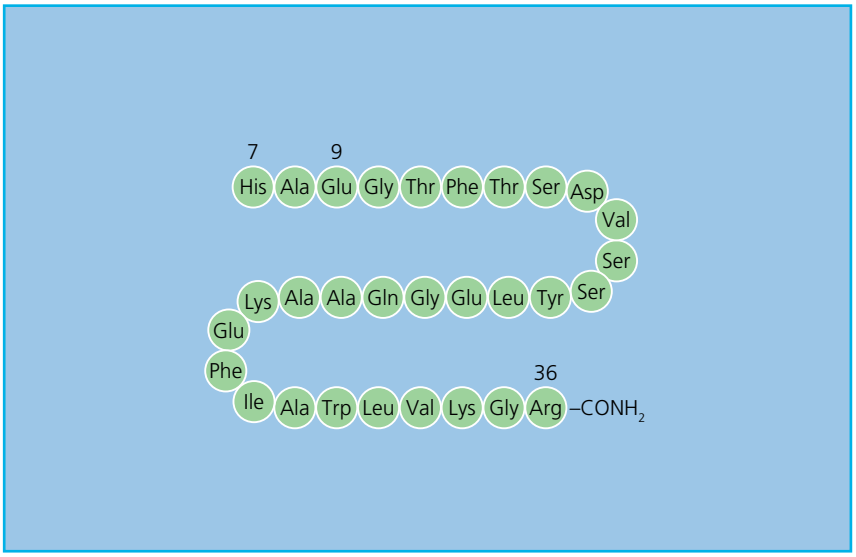

Figure 36.1 Native human glucagon-like peptide 1 (GLP-1) circulates as GLP-1(7–36) amide (illustrated here) or glycine-extended GLP-1(7–37). The enzyme dipeptidyl peptidase 4 (DPP-4) inactivates the hormone by cleaving off the two N-terminal amino acids (His and Ala).

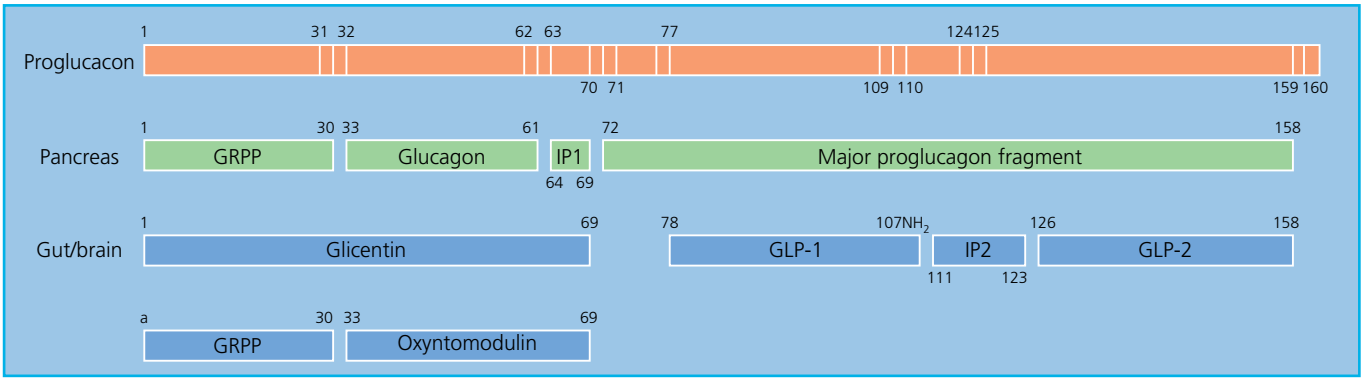

Figure 36.2 Proglucagon processing in human pancreatic α cells (predominantly by prohormone convertase 2) and in enteroendocrine L cells in the small intestine (predominantly by prohormone convertase 1/3). In proglucagon-producing neurons in the nucleus tractus solitarii (brain), proglucagon is most likely predominantly processed by prohormone convertase 1/3 as in the gut. GLP, glucagon-like peptide; GRPP, glicentin-related pancreatic peptide; IP, intervening peptide.

precise mechanisms behind this pathophysiological characteristic remain somewhat controversial. In the 2000s, publications reported reduced secretion of GLP-1 in individuals with type 2 diabetes [22, 23], but recent meta-analyses suggest that the secretion of GLP-1 among people with type 2 diabetes is generally normal [24, 25]. In contrast to the severely reduced insulinotropic effect of GIP in type 2 diabetes [26], the insulinotropic effect of GLP-1 is sustained in these individuals, albeit with reduced potency. Furthermore, GLP-1 retains its glucagonostatic effect in individuals with type 2 diabetes [27, 28].

The reduced incretin effect in type 2 diabetes, the early reports on reduced post-prandial GLP-1 responses, and the preserved glucose-dependent insulinotropic and glucagonostatic effects of GLP-1 constituted important incentives to pursue GLP-1 as a target for the treatment of type 2 diabetes. The other incretin hormone, GIP, was initially not pursued as a glucose-lowering drug owing to its severely diminished insulinotropic effect in type 2 diabetes combined with reports suggesting glucagonotropic effects of GIP. Other studies suggested that GIP may act as a fat storage hormone promoting lipogenesis, adipokine secretion, and weight gain. Nevertheless, as GIP, like GLP-1, is a substrate of DPP-4, it may contribute to the glucose-lowering effect of DPP-4 inhibitors, and dual or even triple hormonal receptor agonists involving GIP receptor stimulation are currently in clinical development for the treatment of type 2 diabetes and other metabolic disorders, such as obesity and non-alcoholic fatty liver disease. The dual GIP/GLP-1 receptor agonist tirzepatide developed for once-weekly subcutaneous injection exerts considerable reductions in glycated haemoglobin (HbA_{1c}) and body weight in individuals with type 2 diabetes and overweight or obesity in its Phase III clinical programme [29].

GLP-1 physiology and anti-diabetes effects

Proglucagon distribution, GLP-1 release, and metabolism

The glucagon gene is expressed in pancreatic α cells as well as in the enteroendocrine L cells and a subset of central nervous system neurons in the nucleus tractus solitarii. The processing of proglucagon into *pancreatic* glucagon or *intestinal* GLP-1 (and GLP-2) depends on tissue-specific prohormone convertases (Figure 36.2). In the pancreas, prohormone convertase 2 represents the predominant

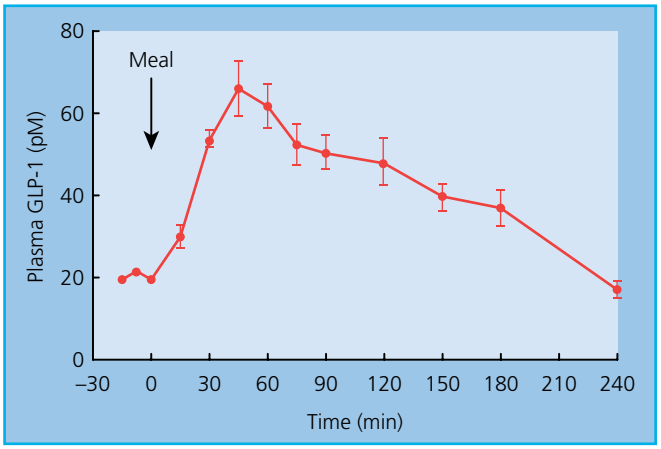

Figure 36.3 Mean post-prandial plasma concentrations (±standard error of the mean) of glucagon-like peptide 1 (GLP-1) in healthy individuals. Source: Based on Sonne et al. 2014 [31].

prohormone convertase and, therefore, glucagon production is favoured. Conversely, in the gut, prohormone convertase 1/3 is abundant and processing of proglucagon predominantly yields the hormones GLP-1 and GLP-2 (and oxyntomodulin) (Figure 36.2). Nevertheless, the distribution of the two prohormone convertases may not be as stringent and their enzymatic specificities may not be as high as previously considered and, thus, small amounts of GLP-1 and GLP-2 may be formed in the pancreas, and similarly, gut-derived glucagon secretion may also occur [30].

The most robust physiological stimulus for GLP-1 secretion is meal ingestion. Within 5–15 minutes of eating, plasma GLP-1 concentrations start to rise, and peak levels are typically reached after 45–60 minutes (Figure 36.3). Fat, carbohydrates, and protein all stimulate GLP-1 secretion. The interaction of nutrients with luminal microvilli of the L cell apical parts results in GLP-1 secretion from the baso-lateral parts into the intestinal bloodstream. In this process, associations between glucose absorption and metabolism within the L cell and GLP-1 secretion have been observed. Furthermore, L cells express several G protein-coupled receptors, which can be activated by short- and long-chain fatty acids, bile acids, and possibly other factors that thereby stimulate GLP-1 secretion. In addition, paracrine (e.g. via somatostatin and GIP) and neurohormonal mechanisms (via vagus and sympathetic

neural activation) have been suggested to contribute to post-prandial GLP-1 secretion.

After secretion, GLP-1 is degraded by the enzyme DPP-4. This enzyme is widely expressed and is highly active in the liver, the intestinal and renal brush border membranes, and the lungs. It is also found on capillary surfaces and in a soluble form in plasma. DPP-4 cleaves off the two N-terminal amino acids of peptides with a penultimate proline or alanine residue, and this completely abolishes the insulinotropic activity of GLP-1. Thus, after secretion of GLP-1, the active hormone is rapidly degraded to an inactive metabolite in the circulation, resulting in a clearance, which exceeds cardiac output, and an apparent half-life of 1–1.5 min. The truncated metabolite is eliminated more slowly through the kidneys and endogenous protease activity, with a half-life of 4–5 min.

GLP-1 receptor distribution and physiological effects of GLP-1

The GLP-1R is found within the pancreas, lung, adipose tissue, kidney, heart, vascular smooth muscle, peripheral nervous system, and several specific nuclei in the central nervous system (CNS) [32, 33]. The exact effect of receptor activation in several of these tissues remains to be established, and here emphasis will be put on receptor activation that relates to the clinical effects observed with GLP-1RA treatment.

Effects on pancreatic insulin and glucagon secretion

Specific receptors for GLP-1 are found in the pancreatic β-cell plasma membrane. The receptor belongs to the glucagon subfamily of G protein-coupled receptors. Following binding and subsequent activation of the receptor, several intracellular pathways are initiated [32, 33], which ultimately results in intracellular accumulation of cyclic adenosine monophosphate, closure of ATP-sensitive K^+ channels, elevation of cytosolic Ca^{2+} concentrations, and mobilization and exocytosis of insulin-containing granules. Importantly, GLP-1R activation in β cells leads only to insulin secretion when glucose concentrations are elevated above 4–5 mmol/l [34]. Thus, GLP-1 can be perceived to act as a β-cell sensitizer potentiating glucose-induced insulin secretion. In addition to its glucose-dependent insulinotropic effect, GLP-1 enhances all steps of insulin biosynthesis and insulin gene transcription. Furthermore, GLP-1 is involved in β-cell growth and differentiation and may protect cells from apoptosis [32, 33]. However, the role of these cell cycle regulatory mechanisms in relation to human physiology and pathophysiology and GLP-1RA treatment remains to be established.

In pancreatic cells, GLP-1 exerts glucagon-suppressive effects. As for its insulinotropic effect, this glucagonostatic effect is glucose dependent and is likewise only active when plasma glucose levels are elevated above 4–5 mmol/l [28]. The mechanisms by which GLP-1 reduces α-cell secretion of glucagon remain incompletely understood. Thus, it is controversial whether GLP-1-induced glucagon suppression is mediated via GLP-1Rs on pancreatic α cells (which have been shown to exist in small amounts in some studies, whereas other studies have not detected them) or whether indirect mechanisms (e.g. via glucagon-suppressive effects of β-cell secretory products and/or somatostatin from pancreatic δ cells) are at play; or perhaps most likely a combination of these effects.

Effects on the gastrointestinal tract

GLP-1 reduces gastrointestinal motility and intermittent GLP-1R activation has a pronounced effect on gastric emptying of both liquid and solid meals [35]. This phenomenon has been referred to as the *ileal brake*; that is, GLP-1 secreted from enteroendocrine cells in the distal small intestine slows further delivery of nutrients to the small intestines from the stomach [36]. GLP-1-induced deceleration of gastric emptying translates into reduced post-prandial plasma glucose excursions [37]. By contrast, prolonged GLP-1R activation leads to tachyphylaxis of this effect [38], which most likely explains the sustained effect of short-acting GLP-1RAs on post-prandial plasma glucose excursions and the lesser effects seen with long-acting GLP-1Ras [39].

Effects on appetite and food intake

GLP-1Rs are found in both the peripheral nervous system and CNS, with GLP-1R-positive neurons in the hypothalamus and the brainstem. The pathways controlling modulation of food intake by GLP-1 are not fully understood, however activation of GLP-1Rs in the brain, specifically the circumventricular organs, is believed to be responsible for the reduced appetite and food intake observed after GLP-1 administration [33]. Nevertheless, modulation of food intake by GLP-1 may also involve vagal afferent neurons. The GLP-1 effect on food intake has been demonstrated in clinical studies, where infusion of GLP-1 in lean individuals and those with obesity with and without diabetes causes dose-dependent reductions in *ad libitum* food intake and increases satiety [40]. However, as GLP-1R knockout mice are not obese, GLP-1R activation is not likely to be a prerequisite for body weight regulation in normal physiology [41]. Nevertheless, GLP-1R activation and its related effects on appetite and food intake constitute an important part of the body weight–lowering effect of pharmaceutical GLP-1RAs [42].

Effects on the cardiovascular system

The effect of GLP-1 on the cardiovascular system has attracted much intention and is amplified by the beneficial effect of GLP-1RAs on cardiovascular disease progression in clinical studies. The GLP-1R is expressed in both the heart atria and ventricles as well as the sinoatrial node [33]. Since most studies have applied supra-physiological GLP-1 doses, the physiological role of the GLP-1R in the heart remains unclear [43]. However, mice lacking the GLP-1R exhibit impaired left ventricular contractility and diastolic function, and also impaired responses to exogenous epinephrine, indicating a role for GLP-1 in cardiac structure and function [44]. Infusion of GLP-1 and GLP-RAs induces an increase in heart rate, which is mediated through both the autonomic nervous system as well as GLP-1R located at the sinoatrial node [45]. Furthermore, some studies have shown that GLP-1 protects the ischaemic and reperfused myocardium in rats [46], improves the ejection fraction in individuals treated with angioplasty after acute myocardial infarction [47], and improves left ventricular function and systemic haemodynamics in dogs with induced dilated cardiomyopathy [48]. GLP-1 reduces the post-prandial rise in triglycerides and lowers free fatty acid concentrations in healthy individuals [49], and improves endothelial dysfunction in individuals with type 2 diabetes and coronary heart disease [50]. Lastly, GLP-1 may exert a beneficial effect on the cardiovascular system through decreased inflammation and oxidative stress [51].

Effects on renal function

GLP-1 increases natriuresis through inhibition of the Na^+/H^+ exchanger in the proximal tubules, which may in part explain why GLP-1RAs have subtle antihypertensive effects [52, 53]. Additionally, GLP-1RA reduces glomerular hyperfiltration and albuminuria in individuals with type 2 diabetes [54]. The exact

localization of the GLP-1R in the kidney remains controversial; however, current evidence suggests that it is expressed in preglomerular afferent arterioles, whereas its presence in tubular and juxtaglomerular cells is uncertain [33]. Whether the natriuretic effect of GLP-1 is exerted directly through renal GLP1-Rs, modulation of the atrial natriuretic peptide or the renin–angiotensin system, or a neural pathway remains unclear.

Neuroprotective effects

Finally, GLP-1 has been associated with improved learning in rats and has also displayed neuroprotective effects, but again human studies have not established GLP-1 as a neuroprotective hormone so far or provided convincing evidence for significant effects of GLP-1R agonism on neurodegenerative diseases [55].

Most of what is known about GLP-1's pleiotropic physiological effects stems from studies of pancreatic islet function, particularly β-cell function. It is well acknowledged that GLP-1-induced insulinotropic and glucagonostatic effects represent the main mediators of the normalization of fasting plasma glucose and diurnal plasma glucose excursions and also improved glycaemic levels observed in studies utilizing native GLP-1 in people with type 2 diabetes [56–59]. Such studies have been of great importance to the development of GLP-1RAs.

GLP-1 receptor agonists for the treatment of diabetes

In 2005, the GLP-1RAs were introduced into clinical practice, and since 2009 they have been included in the joint position statements on the treatment of type 2 diabetes by the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA). Recently GLP-1RAs have been recommended as the first injectable therapy before insulin [60]. The GLP-1RAs, which exert the pleiotropic effects of the native gut hormone GLP-1, target a broad spectrum of the multifaceted pathophysiology of type 2 diabetes, and improve glucose homeostasis with a low risk of hypoglycaemia combined with body weight loss [61,62]. Furthermore, they reduce cardiovascular events [63]. The introduction of the GLP-1RAs has generated substantial clinical interest and they are increasingly prescribed by clinicians worldwide. Until recently, all GLP-1Ras were administrated by subcutaneous injection; however, one GLP-1RA, semaglutide, is now available as an oral formulation, which may facilitate use of this class earlier in the treatment cascade owing to wider acceptance from the individual with type 2 diabetes and healthcare professionals [64].

As several GLP-1RAs have emerged, it has become apparent that there are clinically relevant differences between them, making the therapeutic field challenging to navigate. Currently, seven GLP-1RAs are approved for treating people with type 2 diabetes (Table 36.1) [61,62]. The challenge in developing a GLP-1RA is that native GLP-1 is rapidly degraded by the enzyme DPP-4, resulting in a short half-life (1–2 min) [65]. To overcome this, GLP-1RAs resistant to degradation by DPP-4 have been developed using two different strategies. The first strategy is based on the naturally occurring polypeptide exendin-4, which was originally isolated from the saliva of the lizard *Heloderma suspectum*. Exendin-4 is DPP-4 resistant, but activates the GLP-1R with equal efficacy to native GLP-1. The other strategy is based on the structure of native GLP-1, with a few amino acid alterations that protect the molecule from being degraded by DPP-4. The main difference between the GLP-1RAs resides in the pharmacokinetic profiles that largely divide them into short-acting and long-acting GLP-1RAs (Table 36.1). The differences in similarity to native GLP-1, pharmacokinetics, and molecular size of the GLP-1R agonists are important, as the efficacy and tolerability seem to depend on these differences.

Table 36.1 Pharmacokinetic properties of approved GLP-1RAs.

GLP-1 RAs		Approval year			Pharmacokinetics (single-dose administration)			
Compound	Category	FDA	EMA	Reference amino acid	Time to peak	Half-life	Elimination	Antibody development (% of individuals)
Exenatide twice daily	Short acting	2005	2006	Exendin-4 (53% homology with native GLP-1)	2.1–2.2 h	2.4 h	Mainly renal	35
Lixisenatide	Short acting	2016	2013	Exendin-4 (53% homology with native GLP-1)	~2 h	3 h	Mainly renal	56–70
Liraglutide	Long acting	2010	2009	GLP-1 (97% homology with native GLP-1)	11.0–13.8 h	13 h	Peptide hydrolysis, renal (6%) and faecal (5%)	8.6
Exenatide once weekly	Long acting	2012	2011	Exendin-4 (53% homology with native GLP-1)	NA	2.4 h	Mainly renal	57
Dulaglutide	Long acting	2014	2014	GLP-1 (~90% homology with native GLP-1)	48 h	4.7 d	Peptidases and renal	1.6
Semaglutide	Long acting	2017	2019	GLP-1 (94% homology to native GLP-1)	24 h	7 d	Peptidases and renal	0.01–3.50
Oral semaglutide	Long acting	2019	2020	GLP-1 (94% homology to native GLP-1)	<1–4 h	7 d	Peptidases and renal	0.5

EMA, European Medicines Agency; FDA, US Food and Drug Administration; GLP-1, glucagon-like peptide 1; GLP-1RA, glucagon-like peptide 1 receptor agonist.
Source: Adapted from Andreasen et al. 2021 [62].

Short-acting GLP-1RAs

The short-acting GLP-1RAs are readily absorbed after subcutaneous injection and are resistant to degradation by DPP-4, but are still subject to renal elimination, which confers a plasma half-life of ~2–4 h [66,67]. They are administered twice daily (exenatide) or once daily (lixisenatide), which results in relatively large fluctuations in plasma concentrations during the day, and intermittent activation of GLP-1Rs.

Exenatide twice daily

Exenatide was introduced in 2005 (Byetta®, AstraZeneca, Cambridge, UK) and is a synthetic version of exendin-4, which shares only 53% amino acid sequence homology with human GLP-1 [68,69]. Exenatide is primarily cleared in the kidneys by glomerular filtration [67], and the half-life after subcutaneous injection is ~2.4 h, with detectable plasma concentrations up to 10 h after injection [68]. Exenatide is recommended for twice-daily administration starting at 5 µg twice daily, which may be increased to 10 µg twice daily after one month if well tolerated. To obtain the maximum effect, exenatide should be injected within 60 minutes before the two main meals. The clinical effects of exenatide twice daily were investigated in the AC2993 diabetes Management for Improving Glucose Outcome (AMIGO) trials [69–71]. These trials showed significant reductions in HbA_{1c} versus placebo, and a modest reduction in fasting plasma glucose versus placebo. Post-prandial plasma glucose excursions are blunted in the exenatide-treated participants versus placebo, presumably driven primarily by a substantial deceleration in gastric emptying. Importantly, the effect on post-prandial plasma glucose was only evident during meals with concomitant drug administration; that is, not during lunch where no drug was administered [72]. The average weight loss amounted to 1–4 kg in the exenatide-treated groups versus comparators [73]. The main side effects of exenatide are mild to moderate nausea, diarrhoea, and vomiting [74]. The risk of hypoglycaemia is low with exenatide unless combined with sulfonylurea and insulin.

Lixisenatide once daily

Lixisenatide was approved in 2013 in Europe (Lyxumia®, Sanofi, Paris, France) and in the USA in 2016 (Adlyxin®, Sanofi, Bridgewater, NJ, USA) [75]. As with exenatide, lixisenatide is based on exendin-4, but with a deletion of a proline and an addition of six lysine amino acids at the C-terminus [76]. Clinical trials have demonstrated efficacy and tolerability with a once-daily dose of 20 µg, as evaluated in the clinical trial programme GetGoal [67,77,78]. These trials showed that lixisenatide lowered HbA_{1c} and resulted in moderate reductions of fasting plasma glucose versus placebo. Lixisenatide showed effects on post-prandial plasma glucose during a standardized meal test versus placebo, but only when the drug was administered immediately before food ingestion [74]. A dose-dependent decrease in body weight was seen with the 20 µg once-daily lixisenatide, but in some studies the weight reductions were not superior to placebo [79,80]. The most common side effects of lixisenatide treatment are of gastrointestinal origin (nausea and diarrhoea), consistent with other GLP-1RAs. A head-to-head trial of lixisenatide versus exenatide twice daily reported non-inferiority of lixisenatide regarding HbA_{1c} reduction, slightly better tolerability with nausea, diarrhoea, and vomiting, and fewer episodes of symptomatic hypoglycaemia with lixisenatide. However, lixisenatide treatment was inferior regarding weight loss [77].

Continuous-acting GLP-1RA

Several continuous-acting GLP-RA peptides are available. Different modifications have been applied to prolong the receptor activation. These modifications include:

- Incorporation of the GLP-RA in injectable depot-forming microspheres (exenatide once weekly).
- Attachment of a fatty acid side-chain, which allows reversible binding to albumin (liraglutide and semaglutide).
- Fusion with the Fc fragment of immunoglobulin G (dulaglutide, efpeglenatide).

The longer half-lives of these compounds allow administration with longer intervals, while at the same time reducing fluctuations of plasma peptide levels, resulting in continuous activation of GLP-1Rs [61,62]. Recently, oral semaglutide reached the market, a combination of semaglutide and an absorption enhancer, which protects semaglutide of degradation and facilitates the absorption of semaglutide across the gastric mucosa [81].

Exenatide once weekly

Exenatide was developed as an extended-release formulation approved in Europe in 2011 and in the USA at the beginning of 2012 (Bydureon®, AstraZeneca, Cambridge, UK) [82]. Exenatide once weekly contains exendin-4 encased in microspheres made of biodegradable polymer [83]. The pharmacokinetic profile depends almost solely on the absorption, and over time the biologically active exenatide given as a weekly injection is derived from multiple previous injections undergoing different phases of microsphere dissolution. The extended-release formulation of exenatide once weekly was examined in the phase III clinical trial program Diabetes therapy utilization: researching changes in HbA_{1c} weight and other factors through intervention with exenatide once weekly (DURATION) [84–89]. In two head-to-head studies, it was demonstrated that once-weekly (2 mg) exenatide was superior with regard to glucose lowering to the twice-daily (10 µg) formulation of exenatide, but with similar reductions in body weight [86,88]. Both formulations of exenatide were generally well tolerated; the most frequent adverse event, nausea, was less common with the once-weekly than the twice-daily compound [87]. Once-weekly exenatide 2 mg was also compared in a head-to-head trial with once-daily (1.8 mg) liraglutide [87], with greater reductions in HbA_{1c} and weight loss in the liraglutide-treated group, but once-weekly exenatide was better tolerated [87].

Liraglutide once daily

Liraglutide was approved for clinical use in Europe in 2009 and in the USA in 2010 (Victoza®, Novo Nordisk) [90]. The structure of liraglutide is based on native GLP-1 with an Arg34Lys substitution and the addition of a 16-carbon fatty acid chain at Lys26, leaving liraglutide with a 97% homology with native GLP-1 (Table 36.1). The effects of liraglutide in doses uptitrated to 1.8 mg daily have been investigated in the phase III clinical trial programme Liraglutide Effect and Action in Diabetes (LEAD) [91–97]. Liraglutide significantly lowered HbA_{1c}, fasting plasma glucose, and weight compared with the placebo-treated group. Liraglutide also reduced post-prandial plasma glucose excursions compared with placebo; this effect was, however, primarily mediated by a decrease in pre-prandial (e.g. fasting) glucose values, which is consistent with the observation that liraglutide has small to moderate effects on gastric emptying [97]. The LEAD studies reported significant reductions in systolic blood pressure of up to 6 mmHg, but also a small increase in heart rate of 2–4 beats per minute in the

liraglutide-treated group [95,97]. The most frequently reported adverse events were gastrointestinal (nausea; mild and less persistent compared with treatment with exenatide twice daily) [98]. Compared with exenatide twice daily, liraglutide demonstrated greater reduction in fasting plasma glucose, but weight reductions were equal between the two groups [98]. In a head-to-head trial liraglutide reduced both fasting plasma glucose reductions, HbA_{1c}, and weight more than lixisenatide [99]. Another head-to-head trial with once-daily (1.8 mg) liraglutide demonstrated superiority compared with once-weekly (1.5 mg) dulaglutide with respect to body weight reduction [100].

Dulaglutide once weekly

Dulaglutide (Trulicity®, Eli Lilly and Company, Indianapolis, IN, USA) was approved in 2014 by the FDA and 2015 by the EMA [101]. It comprises two GLP-1 moieties covalently linked to a human immunoglobulin G (IgG) 4-Fc heavy chain, which acts as an inert plasma carrier. Dulaglutide, used as a 1.5 mg once-weekly dose, has been examined in the phase III clinical trial programme Assessment of weekly administration of LY2189265 in diabetes (AWARD), and has also been compared head to head with exenatide twice daily, sitagliptin, and liraglutide [102–104]. Clinical trials showed dose-dependent reductions of HbA_{1c}, fasting plasma glucose, and weight reductions. Safety data indicate a low incidence of hypoglycaemia and the most frequently reported adverse events were gastrointestinal, primarily nausea, which seemed to reduce over time. Dulaglutide 1.5 mg once weekly showed non-inferiority to liraglutide 1.8 mg once daily for HbA_{1c} reduction after 26 weeks, but a greater weight loss was seen in the liraglutide-treated group [100]. As with other GLP-1RA, the most common adverse events are mild to moderate and transient nausea and diarrhoea. Recently, escalation of dulaglutide from 1.5 mg to 3.0 mg or 4.5 mg demonstrated clinically relevant, dose-related reductions in HbA_{1c} and body weight with similar safety profiles, and all three doses are now available for the treatment of type 2 diabetes [105].

Semaglutide once weekly (injection)

Semaglutide once weekly (Ozempic®, Novo Nordisk [106]) was approved in 2018 by the FDA and EMA as a subcutaneously administered GLP-1RA that is structurally closely related to liraglutide, but with the attachment of a C-18 fatty acid chain (instead of the C-16 fatty acid chain in liraglutide) for improved albumin binding. There is also an alanine to α-aminoisobutyric acid substitution at position 8, which decreases degradation by DDP-4. The efficacy and safety of semaglutide in doses uptitrated to 1 mg once weekly were investigated in the phase III clinical trial programme Semaglutide unabated sustainability in treatment of type 2 diabetes (SUSTAIN). Results from the trials support the superiority of semaglutide for reduction of HbA_{1c} and weight loss versus placebo as well as active comparators, including sitagliptin, canagliflozin, exenatide once weekly, dulaglutide, liraglutide, and insulin glargine [107–113]. Interestingly, exposure-response analyses showed a clear relationship reflecting plasma levels of semaglutide obtained after subcutaneous semaglutide and subsequent reductions in HbA_{1c} and body weight [114]. Consistent with these findings, the proportions of people reporting nausea or vomiting with semaglutide subcutaneously were also related to the plasma concentration [114]. The prevalence of gastrointestinal adverse events with once-weekly semaglutide and dulaglutide was similar at a full dose.

Semaglutide once daily (oral)

Oral semaglutide (Rybelsus [115]) was approved in 2019 by the FDA and in 2020 by the EMA. Oral semaglutide is a combination of semaglutide and the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC), which protects semaglutide from degradation in the stomach and facilitates the absorption of semaglutide across the gastric mucosa [64,81]. The efficacy and safety of daily oral semaglutide (3, 7, and 14 mg) were investigated in the phase III clinical trial programme Peptide innovation for early diabetes treatment (PIONEER), which included 10 multinational studies [116–122]. Individuals recruited for this programme were people with type 2 diabetes from across a broad range of disease durations and background therapies, and were representative of many individuals typically encountered in clinical practice. Oral semaglutide 14 mg was superior in reducing HbA_{1c} versus empagliflozin (25 mg) when used as second-line treatment in individuals not reaching their target on metformin [117], and superiority was also seen versus sitagliptin (100 mg) [118]. Oral semaglutide (uptitrated to 14 mg) was non-inferior to subcutaneous liraglutide (1.8 mg once daily) in decreasing HbA_{1c} [119]. Body weight reductions were similar for oral semaglutide compared with empagliflozin [117], but with greater reductions than sitagliptin [118] and liraglutide [119]. These observations suggest that oral semaglutide may provide some weight management benefits versus other commonly prescribed subcutaneous GLP-1RAs. Overall, oral semaglutide is well tolerated, with a safety profile consistent with the GLP-1RA drug class. The risk of hypoglycaemia was low, and the most common adverse events were gastrointestinal, with nausea and diarrhoea generally being the most frequently reported manifestations [64]. Currently higher doses (up to 50 mg) of oral semaglutide are being investigation for the treatment of type 2 diabetes and obesity [123–126].

Albiglutide once weekly

Albiglutide was a once-weekly GLP-1RA for subcutaneous administration approved in 2014 in both the USA (Tanzeum®, GlaxoSmithKline, Durham, NC, USA) and Europe (Eperzan®, GlaxoSmithKline, Brentford, UK), but in 2018 it was withdrawn from the market for commercial reasons.

Efpeglenatide once weekly

Efpeglenatide is a once-weekly exendin-4-based subcutaneously administrated GLP-1RA under development. The modified exendin-4 has been conjugated with an IgG4 Fc fragment to avoid DPP-4 degeneration and renal clearance [127,128]. Efpeglenatide has not yet been approved by the FDA.

Cardiovascular outcome trials with GLP-1RA in diabetes

The cardiovascular safety of all approved GLP-1RAs has been investigated in large-scale cardiovascular outcome trials, except for the short-acting exenatide twice daily, which was approved before cardiovascular outcome trials were mandated by the FDA and EMA (Table 36.2). The cardiovascular outcome trials are international, multicentre, double-blinded, randomized trials, which have compared the cardiovascular effect of GLP-1RAs with placebo when added to standard therapy. All trials have applied the same composite primary endpoint of major adverse cardiovascular events comprising cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, except for the Evaluation of Lixisenatide in Acute Coronary

Table 36.2 Overview of currently published cardiovascular outcome trials including baseline characteristics and outcomes.

	Cardiovascular outcome trials of GLP-1RAs								
Trial drug	**Trial name**	**Year of completion**	**Number of individuals**	**Median follow-up (years)**	**Age (years)**	**HbA_{1c} (%)**	**CVD**	**Exposure to trial drug**	**MACE (HR [95% CI])**
Lixisenatide	ELIXA	Feb 2015	6068	2.1	60	7.7	100%	91%	1.02 (0.89–1.17)
Liraglutide	LEADER	Dec 2015	9340	3.8	64	8.7	81.3%	84%	0.89 (0.78–0.97)
Semaglutide	SUSTAIN 6	Mar 2016	3297	2.1	65	8.7	83.0%	87%	0.74 (0.58–0.95)
Exenatide once weekly	EXSCEL	May 2017	14 752	3.2	62	8.1	73.1%	76%	0.91 (0.83–1.00)
Albiglutide	HARMONY Outcomes	Nov 2017	9463	1.6	64	8.7	100%	87%	0.78 (0.68–0.90)
Dulaglutide	REWIND	Aug 2018	9901	5.4	66	7.3	31.5%	82%	0.88 (0.79–0.99)
Semaglutide (oral)	PIONEER-6	Sep 2018	3183	1.3	66	8.2	84.7%	75%	0.79 (0.57–1.11)
Efpeglenatide	AMPLITUDE-O	Dec 2020	4076	1.8	65	8.9	89.6%	89%	0.73 (0.58–0.92)

CI, confidence interval; CVD, cardiovascular disease; GLP-1RA, glucagon-like peptide 1 receptor agonist; HbA_{1c}, glycated haemoglobin; HR, hazard ratio; MACE, major adverse cardiovascular event.

Syndrome (ELIXA) trial, in which the primary composite endpoint also included hospitalization for unstable angina [61–63].

The ELIXA trial, which investigated the cardiovascular safety of lixisenatide, was the first cardiovascular outcome trial to provide data for a GLP-1RA and the only cardiovascular outcome trial to provide data for a short-acting GLP-1RA [129]. The trial included individuals with type 2 diabetes and recent acute coronary syndrome, and showed that lixisenatide was non-inferior to placebo in reducing the primary composite endpoint. Hence, the available data are currently not supporting any beneficial cardiovascular effect of short-acting GLP-1RAs.

Several continuous-acting GLP-1RAs have proved to reduce major adverse cardiovascular events. The first cardiovascular outcome trials to provide data for continuous-acting GLP1-RAs were the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial and the SUSTAIN 6 trial, which investigated the cardiovascular safety of liraglutide and semaglutide, respectively [130, 131]. These trials included individuals with type 2 diabetes and established cardiovascular disease or high risk of cardiovascular disease. Both liraglutide and semaglutide proved superior to placebo in reducing major adverse cardiovascular events, thereby being the first GLP-1RAs with a proven effect on the prevention of cardiovascular events.

The next cardiovascular outcome trial to present data on the cardiovascular safety of a GLP-1RA was the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial, which also was the largest of the cardiovascular outcome trials with >14 000 participants [132]. The trial was designed to have 70% individuals with pre-existing cardiovascular disease and 30% without cardiovascular disease. In this trial, exenatide once weekly was non-inferior to placebo, but superiority was not proved. The participants in EXSCEL were younger and had a lower HbA_{1c}, a lower prevalence of cardiovascular disease, and a lower time on active treatment during the trial than previous cardiovascular outcome trials, which may partly explain the inability of exenatide once weekly to obtain superiority. Both dulaglutide and albiglutide subsequently were shown to reduce major adverse cardiovascular events in their respective cardiovascular outcome trials [133, 134]. In the Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND) trial, dulaglutide reduced major adverse cardiovascular events in a population with a markedly lower level of established cardiovascular disease at baseline when compared to any of the other cardiovascular outcome trials, which predominantly included individuals with established cardiovascular disease [133]. This finding supports a role for dulaglutide and potentially the other continuous-acting GLP-1RAs in the primary prevention of cardiovascular disease in type 2 diabetes.

The PIONEER-6 trial investigating the cardiovascular safety of oral semaglutide included the smallest population and had the shortest follow-up time of the completed cardiovascular outcome trials [135]. Oral semaglutide demonstrated non-inferiority, but not superiority, compared with placebo. The estimated hazard ratio of major adverse cardiovascular events was roughly like that of subcutaneous semaglutide, but with a markedly wider confidence interval, and hence the study was likely underpowered to detect any significant effect. Whether oral semaglutide has a beneficial cardiovascular effect remains to be explored in the ongoing Heart Disease Study of Semaglutide in Patients with Type 2 Diabetes (SOUL) trial [136]. The last of the cardiovascular outcome trials to be completed was the Effect of Efpeglenatide on Cardiovascular Outcomes (AMPLITUDE-O) trial, which investigated the cardiovascular safety of efpeglenatide and included individuals with type 2 diabetes and established cardiovascular disease or current kidney disease plus a least one cardiovascular risk factor [128]. This was the first trial to demonstrate a significant reduction in major adverse cardiovascular events for an exendin-4-based GLP-1RA.

Whereas the currently conducted cardiovascular outcome trials support a class effect for continuous-acting GLP-1RAs on the risk of cardiovascular disease, the trials have revealed an inconsistent effect on the individual major adverse cardiovascular event components. However, in a meta-analysis of the currently published cardiovascular outcome trials including >60 000 individuals, a significant effect on each of the components (cardiovascular death, fatal or non-fatal myocardial infarction, and fatal or non-fatal stroke) was found [63]. The meta-analysis also found that treatment with a GLP-1RA reduced the risk of hospitalization for heart failure.

It is important to recognize that the populations in the cardiovascular outcome trials are different and results from the different trials cannot be directly compared. The prevalence of established cardiovascular disease varied from 32% to 100%, which affected the incidence of major adverse cardiovascular events and thereby the number needed to treat. However, in a meta-analysis, the number needed to treat to prevent one incident major adverse cardiovascular event over a weighted average median follow-up period of three years was 65 individuals [63].

In addition to investigating the effect of GLP-1RAs on cardiovascular disease, most cardiovascular outcome trials have included renal secondary endpoints. Treatment with GLP-1RA reduced a broad composite renal outcome comprising development of macroalbuminuria, doubling of serum creatinine, or at least 40% decline in estimated glomerular filtration rate (eGFR), kidney replacement therapy, or death due to kidney disease [137]. However, this effect was mainly driven by a decrease in macroalbuminuria, and whether GLP-1RAs reduce worsening in kidney function and delay progression to dialysis is still to be determined. Nevertheless, in a sensitivity analysis excluding data from the ELIXA trial, which stands out as the only cardiovascular outcome trial investigating a short-acting GLP-1RA, treatment with GLP-1RAs led to a significant reduction of 18% in worsening of kidney function, defined as either doubling of serum creatinine or ≥40% decline in eGFR [63].

Safety Issues

The safety of GLP-1RAs has been extensively studied in pre-clinical studies, the large clinical trial programmes, as well as the cardiovascular outcome trials. The most common adverse events observed in clinical trials of GLP-1RAs involve the gastrointestinal system and are mainly nausea, vomiting, and diarrhoea. These events are dose dependent and diminish over time. Differences exist in the reported occurrence of these gastrointestinal effects between each GLP-1RA. Other identified potential safety issues include hypoglycaemia, pancreatic adverse events, thyroid neoplasms, immunogenicity issues, and interactions with other medicinal products [68, 75, 82, 90, 101, 106, 115].

Hypoglycaemia

GLP-1RAs generally confer a low risk of severe hypoglycaemia, as the clinical insulin-stimulatory effects are only present at plasma glucose levels >4 mmol/l (72 mg/dl) [138]. In monotherapy or combination with other anti-diabetes agents that have a low risk of hypoglycaemia (e.g. metformin), the GLP-1RAs uncommonly cause hypoglycaemia [68, 75, 82, 90, 101, 106, 115]. In trials in which the GLP-1RAs were combined with a hypoglycaemic agent, such as a sulfonylurea or insulin, the incidence of non-severe hypoglycaemia was significantly higher (up to one-third of participants), depending on trial duration, study population, and the dose of insulin and/or sulfonylurea. When a GLP-1RA has been combined with insulin treatment in clinical trials, symptomatic hypoglycaemic events have been reported in ~25% of individuals, and slightly more with short-acting than continuous-acting GLP-1RAs [139].

Pancreatic adverse events

Since the introduction of GLP-1-based therapy, pancreatic adverse effects, in particular pancreatitis and pancreatic cancer, have been a major concern. The concern for pancreatic safety was spurred by post-marketing reports of pancreatitis during GLP-1RA treatment. According to an analysis based on the FDA adverse event reporting database for the years 2005–2009 [140], pancreatitis was reported as an adverse event more than six times as frequently for individuals administered exenatide compared with other (non-GLP-1-based) therapies for type 2 diabetes. This may have been a so-called Weber effect, which constitutes a peak in adverse event reporting at the end of the second year after regulatory approval of a drug followed by a continuous decline thereafter [141]. In 2013–2014, the EMA and FDA undertook an extensive appraisal of the existing pre-clinical and clinical safety data together with the observational evidence. They concluded that data were too inconsistent to establish a certain connection between GLP-1RA administration and pancreatic adverse effects, but owing to the uncertainty of the estimates, a causal role could not be completely excluded [142]. A major issue in relation to the spontaneous reports of pancreatic adverse events is the fact that people with type 2 diabetes generally have an up to four times higher risk of pancreatitis than those without diabetes [143]. In contrast to early increases in spontaneously reported events, acute pancreatitis and pancreatic cancer events have been extremely rare in the randomized clinical trials with the GLP-1RAs [144]. Data from cardiovascular outcome trials with adjudicated pancreatic events showed that the incidence of pancreatitis was similar (~0.3%) in GLP-1RA- and placebo-treated individuals with type 2 diabetes [130, 144, 145]. It is important for the interpretation that individuals with a high risk of pancreatitis (e.g. previous pancreatitis) were excluded from participating in most of these trials. Reassuringly, a recent meta-analysis of 22 population-based observational studies did not identify an association with GLP-1RA use and any pancreatic pathology [146]. Nonetheless, acute pancreatitis is still listed as an adverse event for all GLP-1RAs [68, 75, 82, 90, 101, 106, 115]. So far there are no data to suggest differences in adverse pancreatic effects between the GLP-1RAs (e.g. between short- and continuous-acting agents [147]). Individuals started on treatment with any of the GLP-1RAs should be informed of the potential risk and characteristic symptoms of acute pancreatitis; and caution is advised when prescribing GLP-1RAs to those with a risk of or a history of pancreatitis [68, 75, 82, 90, 101, 106, 115].

Thyroid adverse events

The pre-clinical development programme of several GLP-1RAs exposed significant increases in medullary thyroid carcinoma (thyroid C-cell neoplasm) in rodents [68, 75, 82, 90, 101, 106, 115]. The fact that these C-cell neoplasms were not detected in monkeys [148] suggests important species differences. Accordingly, in comparison with rodent thyroid glands, C cells are much less abundant in human thyroid tissue and, equally importantly, GLP-1Rs are present in much lower amounts per C cell [148]. Thyroid events and medullary thyroid carcinoma were closely monitored in the clinical trial programmes of all GLP-1RAs, including their cardiovascular outcome studies and in post-marketing surveillance. The collective evidence does not suggest that GLP-1RA treatment causes a higher risk of thyroid cancers in humans [144, 146, 149].

Immunogenicity issues

The GLP-1RAs are large molecules that can raise an immune response. This is evidenced by measurable levels of antibodies directed against epitopes on the GLP-1RA in some individuals. Generally, the exendin-4-based GLP-1Ras (exenatide, lixisenatide, and efpeglenatide) raise more antibodies (~25–74% of treated

individuals) than the GLP-1RAs with higher peptide sequence homology to native human GLP-1 (liraglutide, semaglutide, albiglutide, and dulaglutide), where antibodies can be detected in 1–9% of those treated. There is conflicting evidence on the clinical relevance of these antibodies [150–152]. However, the presence of high levels of neutralizing antibodies may limit the clinical effects of at least some of the GLP-1RAs (as is evident with exenatide, where high levels are present in 1–6% of individuals, associated with a lower clinical efficacy [151, 153]). Hypersensitivity reactions and local injection-site reactions are inconsistently reported in the trials, but may also depend on immunogenicity. Injection-site reactions include local nodule formation, redness, or itching that occurs in 0–22% of individuals treated with a GLP-1RA for up to a year. Interestingly, injection-site reactions are more frequent in individuals who develop antibodies [82]. However, other excipients in the drug formulation (e.g. the prolonged-release delivery systems in the GLP-1RA for once-weekly administration or fatty acid side-chains to the GLP-1-moeity) may also be important factors in the development of injection-site reactions. Thus, exenatide once weekly caused much more injection site pruritus than exenatide twice daily (18% vs 1%) [88] and injection-site reactions occurred in more individuals given albiglutide than in those given liraglutide (13% vs 5%) [154].

Interactions with other medical products

None of the GLP-1RAs interacts with the hepatic metabolism of other medicinal products; specific interactions with acetaminophen, digoxin, oral contraceptives, lisinopril, metformin, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, and warfarin have been studied in clinical trials [68, 75, 82, 90, 101, 106, 115]. However, all the GLP-1RAs delay gastric emptying with acute dosing, and therefore have the potential to prolong the absorption of concomitantly administered oral medicinal products. Importantly, the effect on gastric emptying diminishes with time for the continuous-acting GLP-1RAs owing to rapid tachyphylaxis, already evident from the first day of treatment [38]. Therefore, the interaction through delayed gastric emptying is mainly of clinical relevance with the short-acting GLP-1RAs and in a situation with concomitant administration of medicinal products with a narrow therapeutic–toxic ratio that require careful clinical or biochemical monitoring. The interaction can be alleviated by administration of the other medicinal product one hour before or four hours after the administration of the short-acting GLP-1RA [68, 75].

Amylin and amylin analogues

Historical overview

Amyloid deposits were discovered a century ago and are described as a pathological feature of people with diabetes and those with insulinomas. In 1987, amylin was isolated from amyloid deposits and there was speculation on whether it had important endocrine effects [155, 156]. Amylin is stored and secreted with insulin from the β cells [157] and type 1 diabetes is considered an amylin-deficient state owing to β-cell destruction, and the hormones exhibiting complementary roles in the regulation of plasma glucose [158]. The physiological actions of amylin involve inhibition of appetite and gastric emptying, and may also involve suppression of glucagon secretion in relation to meal intake [158]. The development of amylin analogues focuses on the clinically beneficial effects on glycaemic levels, especially post-prandially, and body weight in the treatment of diabetes.

Amylin physiology

Amylin release, metabolism, regulation of secretion and receptor

Amylin and insulin are stored together in secretory granules and are co-released from the pancreatic β cells [159]. The release of amylin is stimulated by nutrient ingestion and gut-derived incretin hormones (GLP-1 and GIP) and through neural signalling. Amylin is released during meals and together with insulin in a corresponding high-frequency pulsatile pattern, but at a 1:100 ratio [159]. Deviation from this secretion pattern has been observed in several conditions, including diabetes and obesity, but the mechanisms of the altered amylin secretion pattern and its potential implications are unknown [160]. In contrast to insulin, which is eliminated primarily in the liver, amylin is eliminated mainly through renal metabolism [158]. Amylin acts on a composite receptor with two parts. The *core* part comprises a calcitonin receptor, which is a transmembrane class B G protein-coupled receptor [161, 162]. Two splice variants of the calcitonin receptor (a and b) exist, and they are complexed with one of three receptor activity-modifying proteins (RAMP1, RAMP2, and RAMP3), creating diverse amylin receptors (AMY1, AMY2, and AMY3) [163]. Amylin appears to bind with high affinity to six different emerging receptors [162].

Amylin's effect on gastric emptying and central effects on appetite and food intake

Amylin and GLP-1 share overlapping physiological properties. Both peptide hormones slow nutrient delivery to the small intestine by decelerating gastric emptying, suppress post-prandial glucagon secretion, and reduce appetite, albeit through seemingly different pathways [164]. Dose–response studies performed in rats investigating the influence on gastric emptying exerted by several different subcutaneously injected gastrointestinal hormones (amylin, cholecystokinin octapeptide [CCK-8], GIP, GLP-1, glucagon, and pancreatic peptide) showed that amylin was the most potent inhibitor of these [165]. Correspondingly, subcutaneous injection of a selective amylin receptor antagonist in rats revealed an acceleration of gastric emptying [166, 167]. Importantly, the ability of amylin to inhibit gastric emptying is overridden by the occurrence of hypoglycaemia [168]. Whether amylin's decelerating effect on gastric emptying contributes to its anorectic effects remain uncertain. Nevertheless, exogenous amylin reduces meal size and, furthermore, peripherally or centrally infused amylin receptor antagonist produces an opposite effect, suggesting that amylin is a physiological regulator of food intake [169].

Amylin exerts its anorectic actions via direct effects on the CNS [164, 169, 170]. c-Fos expression (a marker of neuronal activity) is induced by amylin in target neurons in different brain regions involved with metabolic regulation [171]. The area postrema located in the hindbrain is the primary and most important site of amylin action. This assumption is based on studies of rodents undergoing area postrema ablation, which demonstrated a complete abrogation of amylin's anorexigenic effects [172, 173]. After area postrema activation, the amylin signal is conveyed to the

forebrain via distinct relay stations and to regions of hypothalamus known to be involved in feeding behaviour. Within the lateral hypothalamic area, amylin diminishes the expression of orexigenic neuropeptides such as orexin and melanin-concentrating hormone [160, 171, 173]. The area postrema is favourably located as a target of central hormone action owing to the permeable blood–brain barrier in this region. Other brain sites suggested to be important contributors to amylin's anorexic effects include the subfornical organ, the nucleus accumbens, and the dorsal raphe of the brainstem [172, 173]. Amylin's anorectic effect relies on both satiety-promoting effects and attenuation in feeding reward neurocircuits [174]. Whether amylin also exerts peripheral actions has been investigated in muscle, liver, and adipose tissue of mice and adipose tissue of humans [175, 176], and physiological effects were clearly evident with stimulation of distinct signalling pathways after application of amylin. However, the presence of amylin receptors in these peripheral tissues remains uncertain.

Amylin analogues for the treatment of diabetes

The discovery of amylin's glucose and body weight–lowering effects makes it attractive for therapeutic purposes. However, the instability and propensity to self-aggregate complicated the clinical development of drugs based on native sequence human amylin [157]. The problem was solved by substituting a few amino acids in the rat sequence of amylin with proline residues [164]. This enhanced the solubility and markedly reduced amyloid fibril formation of the bioactive peptide [177]. The actions and pharmacokinetic and pharmacodynamic properties of a synthetic amylin analogue, pramlintide, are very similar to those of native amylin [157]. Numerous clinical trials tested the efficacy and safety of pramlintide ahead of its approval by the FDA in 2005. Currently, this sole available amylin analogue is marketed in the USA as Symlin® (Amylin Pharmaceuticals, San Diego, CA, USA). The drug is approved for adjunct treatment of type 1 diabetes and type 2 diabetes, when optimal glucose levels are not achieved with insulin administration alone or combined with other glucose-lowering drugs [178]. Pramlintide is administered in conjunction with meal-time insulin therapy [177]. The plasma elimination half-life is ~48 min when injected subcutaneously in the thigh or the abdomen. The drug is primarily eliminated by the kidneys, like native amylin [179]. The most common adverse events related to pramlintide treatment are of gastrointestinal origin, including decreased appetite, vomiting, and stomach pain, with mild-to-moderate nausea being most frequent. However, these effects are generally transient and can be minimized by slow uptitration. No clear correlation between gastrointestinal symptoms and therapy-induced weight loss has been found [180]. Although pramlintide is well tolerated overall, it is associated with an increased risk of insulin-induced severe hypoglycaemia, particularly in people with type 1 diabetes [181].

Clinical studies investigating the acute and short-term effects of pramlintide have demonstrated reductions in post-prandial glucose excursions and 24 h glucose profile [182]. These glycaemic improvements were observed in acute studies and with continued dosing for 2–4 weeks and are likely due to decreased gastric emptying. Whether amylin-induced attenuation of post-prandial glucagon release contributes remains uncertain. Several larger long-term trials with pramlintide have also been conducted. Hollander et al. investigated HbA_{1c} and weight management with adjuvant pramlintide therapy in 656 individuals with type 2 diabetes with HbA_{1c} ≥8% (64 mmol/mol) who were requiring insulin treatment either alone or combined with oral anti-diabetes medications at baseline [158]. Participants were randomized to receive pramlintide at different doses or placebo for 52 weeks. Treatment with pramlintide twice daily led to a reduction from baseline in HbA_{1c} of −0.62% (7 mmol/mol) at week 52 (vs −0.25% [3 mmol/mol] with placebo). Body weight change at week 52 from baseline was sustained in individuals receiving 120 µg twice daily (−1.4 kg) versus 90 µg twice daily (−0.5 kg) or placebo (+0.7 kg) [158]. The 1155 participants with type 2 diabetes and body mass index >25 kg/m^2, who received pramlintide 120 µg twice daily in the study, were included in a pooled *post hoc* analysis with corresponding participants from another large-scale trial [154, 183]. Significant reductions in both HbA_{1c} (−0.43%; 5 mmol/mol) and body weight (−2.0 kg) from baseline to week 26 (compared with placebo) were found with adjunctive pramlintide therapy. These data indicate that pramlintide added to insulin therapy yields further reductions in HbA_{1c} and a concomitant weight loss in individuals with type 2 diabetes.

Perspectives for non-insulin parenteral therapies

Evidence from large-scale trials focusing on cardiovascular safety has established GLP-1RA as a cornerstone in type 2 diabetes treatment. In contrast to older anti-diabetes agents, several GLP-1RAs confer substantial body weight loss and prevent cardiovascular morbidity and death within few years of initiating therapy in type 2 diabetes. Based on these extraordinary results, the future use of the GLP-1RAs is likely to expand. Two GLP-1RAs (liraglutide and semaglutide) have been approved in higher doses for the treatment of obesity and new avenues for type 2 diabetes–associated conditions are also being specifically investigated. Thus, trials are ongoing in type 2 diabetes–associated chronic kidney disease [184], eye disease [185], and heart failure with preserved ejection fraction [186], but also type 1 diabetes [187] and non-alcoholic fatty liver disease and non-alcoholic steatohepatitis [188]. In addition, potential effects on neurological diseases such as Alzheimer disease [189], Parkinson disease [190], and depression [191] are also possible and are currently being investigated.

When treating complicated metabolic diseases, such type 2 diabetes, intervening with more than one regulatory pathway is often desirable due to additive effects. Along these lines, several dual and/or triple receptor agonists, where activation of the GLP-1R is combined with activity at other peptide hormone receptors, are in clinical development. The combined agonism of GLP-1R and the GIP, glucagon, or amylin receptors is particularly promising and several unimolecular multiagonist treatment compounds simultaneously activating two or more of these receptors, besides the GLP-1R, are in late clinical development for the treatment of type 2 diabetes, obesity, and/or non-alcoholic steatohepatitis [192, 193]. Major caveats for the success of these compounds include the unclear translation to clinical efficacy and safety in humans, and an aggravated risk of untoward immunological reactions and unforeseen off-target effects, which have to compare favourably to the well-established clinical efficacy and safety of optimally dosed GLP-1RAs.

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37 How to Use Type 2 Diabetes Treatments in Clinical Practice

Thomas Karagiannis[1,2], Aris Liakos[1,2], and Apostolos Tsapas[1,2,3]

[1] Diabetes Centre, Second Medical Department, Aristotle University of Thessaloniki, Thessaloniki, Greece

[2] Clinical Research and Evidence-Based Medicine Unit, Second Medical Department, Aristotle University of Thessaloniki, Thessaloniki, Greece

[3] Harris Manchester College, University of Oxford, Oxford, UK

Key points

- Numerous pharmacological options for the management of type 2 diabetes are available.
- The choice of appropriate anti-diabetes therapy is guided by the presence of clinically important comorbidities and underlying cardiovascular risk.
- Sodium–glucose cotransporter-2 (SGLT-2) inhibitors are the treatment of choice in people with heart failure or chronic kidney disease.
- Specific SGLT-2 inhibitors or glucagon-like peptide-1 receptor agonists (GLP-1RAs) are prioritized in people with established or at high risk of developing atherosclerotic cardiovascular disease.
- In those with low absolute cardiovascular risk, therapeutic decisions should consider the efficacy and safety profile of potential agents and avoid increased treatment burden.
- In the presence of obesity, GLP-1RAs or SGLT-2 inhibitors are preferred.
- In those with non-alcoholic steatohepatitis (NASH), pioglitazone and some GLP-1RAs are recommended.
- For treatment of hyperglycaemia, metformin remains the initial choice in most people, including those with newly diagnosed type 2 diabetes, due to the extensive experience with its use, overall efficacy and safety profile, and affordability.
- Additional important considerations affect real-life therapeutic decisions and the likelihood that people will take their medication as prescribed, including the values and preferences of the informed individual, tolerability issues, practical matters, and drug availability and affordability.
- Clinicians should continually update their knowledge of the pharmacological management of type 2 diabetes and avoid clinical inertia by regularly reassessing the overall clinical profile of those they treat.

In recent years, pharmacotherapy for type 2 diabetes has departed from focusing solely on the management of hyperglycaemia to mitigation of cardiovascular risk [1–3]. The changing landscape in the management of type 2 diabetes was largely imposed by findings from cardiovascular outcomes trials, which suggest a beneficial effect on hard clinical endpoints for certain classes of anti-diabetes agents, namely sodium–glucose cotransporter 2 inhibitors (SGLT-2) and glucagon-like peptide 1 receptor agonists (GLP-1RAs). In this context, clinicians should consider indicators of high risk of, or established, atherosclerotic cardiovascular disease, chronic kidney disease, or heart failure when choosing the optimal treatment. In this chapter, we review the main glucose-lowering drug classes in terms of their benefits and harms, and their current place in the management of type 2 diabetes.

Therapeutic options

The number of diabetes drugs has expanded substantially over the preceding years and evidence from cardiorenal outcomes trials is rapidly accruing at a pace that practising clinicians might find hard to follow (Chapters 35 and 36; Table 37.1). Medications approved for the treatment of type 2 diabetes fall into the following main categories:

- Insulin-sensitizing agents, which include biguanides represented solely by metformin, as well as thiazolidinediones represented by pioglitazone; the use of rosiglitazone has practically ceased due to concerns about an increased risk of myocardial infarction [4].
- Insulin secretagogues (sulfonylureas, meglitinides).
- Incretin mimetics (dipeptidyl-peptidase 4 [DPP-4] inhibitors, GLP-1RAs, dual glucose-dependent insulinotropic polypeptide [GIP] and GLP-1RAs).
- Agents that induce glycosuria (SGLT-2 inhibitors).
- Agents that block intestinal absorption of carbohydrates (α-glucosidase inhibitors).
- Insulin.

There are also other medications with glucose-lowering properties (e.g. bile acid sequestrants, dopamine-2 agonists, and amylin mimetics) that are either licensed for the treatment of type 2 diabetes only in specific regions or whose use in clinical practice is very limited.

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Table 37.1 Characteristics of agents used for the treatment of type 2 diabetes in the USA or Europe.

Class	Medications	Primary physiological action(s)	Main advantages	Main disadvantages
Biguanides	Metformin	↓ Hepatic glucose production ↑ Glucose uptake in peripheral tissues	Extensive experience No hypoglycaemia Weight neutral (potential for modest loss) ? Reduction in CV events or all-cause mortality Low cost	Gastrointestinal adverse events Vitamin B_{12} deficiency Contraindicated with eGFR <30 ml/min/1.73 m^2 Lactic acidosis (rare)
Sulfonylureas	Glibenclamide (or glyburide) Gliclazide Glipizide Glimepiride	↑ Insulin secretion	Extensive experience ↓ Microvascular complications Low cost	Hypoglycaemia ↑ Weight Dose adjustment/avoidance in CKD ? Cardiovascular safety 'Pancreatic exhaustion'
Meglitinides (or glinides)	Nateglinide Repaglinide	↑ Insulin secretion	↓ Post-prandial glucose excursions Dosing flexibility Relatively safe in advanced CKD	Hypoglycaemia ↑ Weight ? Cardiovascular safety
Thiazolidinediones (or glitazones)	Pioglitazone	↑ Insulin sensitivity	No hypoglycaemia ↓ Cardiovascular events ↓ Liver steatosis	↑ Weight ↑ Fractures Oedema/heart failure Bladder cancer
DPP-4 inhibitors (or gliptins)	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Glucose dependent: ↑ Insulin secretion ↓ Glucagon secretion	No hypoglycaemia Weight neutral Well tolerated	Modest glycaemic efficacy Skin reactions ↑ Hospitalizations for heart failure (saxagliptin) Dose adjustment in CKD (except for linagliptin) ? Pancreatitis, pancreatic neoplasms ? Arthralgia
GLP-1 receptor agonists	Dulaglutide Exenatide Exenatide LAR Liraglutide Lixisenatide Subcutaneous semaglutide Oral semaglutide	Glucose dependent: ↑ Insulin secretion ↓ Glucagon secretion Delay gastric emptying ↑ Satiety	No hypoglycaemia ↓ Weight ↓ Post-prandial glucose excursions ↓ CV events Prevent progression of albuminuria ↓ Liver steatosis ↓ Mortality	Injectable (except oral semaglutide), local site reactions, require training Gastrointestinal adverse events ? Pancreatitis, pancreatic neoplasms Gallbladder disease ? Medullary carcinoma ↑ Heart rate High cost
GIP/GLP-1 receptor agonists	Tirzepatide	Glucose dependent: ↑ Insulin secretion ↓ Glucagon secretion Delay gastric emptying ↑ Satiety Improve lipid homeostasis ↑ Insulin sensitivity	No hypoglycaemia ↓ Weight	Injectable Gastrointestinal adverse events High cost Currently in development
SGLT-2 inhibitors (or gliflozins)	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Insulin independent inhibition of glucose reabsorption in the proximal convoluted tubule ➔ glucosuria	No hypoglycaemia ↓ Weight ↓ Blood pressure ↓ CV events in high-risk individuals ↓ Hospitalizations for heart failure Prevent progression of CKD ↓ Mortality	Genitourinary tract infections Volume depletion (dizziness, orthostatic hypotension, syncope) esp. in older people, CKD, or those on diuretics Dose adjustment in CKD (see labels of individual agents for renal dose considerations) Lower glycaemic efficacy at low eGFR ↑ Risk for amputation (canagliflozin) ↑ Risk for fracture (canagliflozin) Euglycaemic ketoacidosis (rare) High cost

(*continued*)

Table 37.1 (*Continued*)

Class	Medications	Primary physiological action(s)	Main advantages	Main disadvantages
Insulins	Basal • Human NPH • Detemir • Degludec (U-100 and U-200) • Glargine (U-100, U-300, and biosimilars) Prandial • Human regular • Aspart (including faster acting) • Glulisine • Lispro (U-100, U-200, and ultra-rapid) Premixed	↑ Glucose disposal ↓ Hepatic glucose production	Nearly universal response Theoretically unlimited efficacy ↓ Microvascular complications	Hypoglycaemia ↑ Weight Injectable, require training Frequent self-monitoring and dose adjustment High cost (insulin analogues) Treatment burden may lead to reluctance to take insulin

CKD, chronic kidney disease; CV, cardiovascular; DPP-4, dipeptidyl-peptidase 4; eGFR, estimated glomerular filtration rate; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; LAR, long-acting release; NPH, neutral protamine Hagedorn; SGLT-2, sodium–glucose cotransporter 2.

Metformin

Metformin is an oral biguanide that first received marketing approval in Europe in 1957 and the USA in 1994; it has the advantage of targeting insulin resistance, which is considered an early feature of type 2 diabetes. It acts mainly by suppressing gluconeogenesis in the liver, thereby reducing hepatic glucose production. Moreover, it leads to increased peripheral glucose uptake mainly in skeletal muscles, possibly by enhancing the binding of insulin to its receptors. It appears to be ineffective in tissues that are insensitive to insulin such as the brain [5]. Several other physiological effects have also been described, such as decreased fatty acid oxidation and increased intestinal glucose use, potentially mediated by release of intestinal GLP-1. About 90% of the drug is eliminated in the urine.

The maximal daily dose of metformin is 3000 mg in Europe or 2550 mg in the USA and the drug is usually administered in 2–3 divided doses that are taken with meals. To improve gastric tolerance the drug should be introduced at a dose of 500 or 850 mg twice daily, which should be adjusted slowly in biweekly intervals. Given the rising rates of obesity and the associated prevalent cases of type 2 diabetes among younger individuals, use of metformin is now allowed in children from 10 years of age, but the maximum recommended dose for the paediatric population is 2000 mg. Extended-release formulations for once-daily dosing and fixed-dose combinations with other oral anti-diabetes agents are available.

Metformin is contraindicated in severe renal impairment with an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2. In Europe, the daily dose of metformin should not exceed 2000 mg for those with stage 3A chronic kidney disease (eGFR 45–59 ml/min/1.73 m^2), whereas for individuals with stage 3B chronic kidney disease (eGFR 30–44 ml/min/1.73 m^2) the maximal daily metformin dose is 1000 mg. In the USA, initiation of metformin is not recommended with an eGFR between 30 and 45 ml/min/1.73 m^2. Annual monitoring of serum creatinine is required and people with moderate renal impairment should be educated to withhold metformin during acute illness or if the administration of iodinated contrast media is planned.

Experience with metformin is extensive and no major safety concerns have arisen to date. Metformin does not increase the risk of hypoglycaemia and can have a small effect to reduce body weight [6]. Because of its favourable efficacy, safety profile, and low cost, it is generally considered as first-line therapy for most people with type 2 diabetes unless contraindicated or not tolerated. Intensive treatment with metformin was also associated with a lower incidence of all-cause mortality compared to diet in people with overweight and newly diagnosed type 2 diabetes in a substudy of the UK Prospective Diabetes Study (UKPDS) [7,8]. However, in another substudy that was also performed within the UKPDS, addition of metformin to sulfonylurea resulted in increased mortality compared with sulfonylurea alone [7]. No firm explanation could be given for this controversial finding, and based on later follow-up data it was attributed to chance [9]. A meta-analysis incorporating data from both UKPDS substudies and additional smaller randomized controlled trials found a neutral effect of metformin on all-cause mortality [10]. Consistently, metformin had no effect on major cardiovascular events over a 21-year median follow-up of participants in the Diabetes Prevention Program (DPP) and Diabetes Prevention Program Outcomes Study (DPPOS) [11].

Metformin is commonly associated with gastrointestinal side effects including metallic taste, bloating, abdominal discomfort, and soft bowel movements or diarrhoea. These symptoms may improve over time and can be mitigated by gradual dose titration. The most concerning safety issue is metformin-associated lactic acidosis. This extremely uncommon but potentially life-threatening condition usually develops in the setting of critical illness that predisposes to hypoperfusion or hypoxaemia, including renal insufficiency, liver disease, and shock, or as a result of drug overdose. Finally, metformin reduces vitamin B_{12} absorption in the small intestine, which might present as peripheral neuropathy, although the drug rarely causes megaloblastic anaemia. Clinicians might offer periodic monitoring of serum vitamin B_{12} concentrations, especially for high-risk people such as those on a vegan diet or after bariatric surgery [12].

Sulfonylureas

Sulfonylureas are the oldest class of oral anti-diabetes compounds. They bind to sulfonylurea receptors in pancreatic β cells and stimulate insulin release by inhibiting adenosine triphosphate (ATP)-sensitive potassium channels, leading to depolarization of the cell membrane, which in turn results in calcium influx and consequent exocytosis of insulin. Because they constantly stimulate insulin secretion, sulfonylureas are very effective in terms of glycated haemoglobin (HbA_{1c}) lowering, especially at early stages of the disease in people with residual β-cell function. Nevertheless, sulfonylureas are associated with a lack of a durable effect on glucose lowering, which is related to the declining insulin-producing capacity of β cells, a phenomenon known as *pancreatic exhaustion*. First-generation agents are no longer used in clinical practice and have been replaced by second-generation sulfonylureas including gliclazide (also available as a modified-release formulation), glipizide, glibenclamide (also known as glyburide), and glimepiride (also classified as a third-generation sulfonylurea), which have a prolonged duration of action and more convenient dosing scheme [13].

Hypoglycaemia is a major limitation of this class, because sulfonylureas increase insulin release irrespective of blood glucose concentrations. Hypoglycaemia might be prolonged and require hospitalization. It is more likely to occur after exercise or in the fasting state. Because sulfonylurea metabolites are renally excreted, the risk of hypoglycaemia is higher in people with chronic kidney disease. Hence, the drugs should be initiated at the lower end of the approved dose range and carefully titrated, especially in older individuals or those with chronic kidney disease.

Sulfonylureas should also be given with caution or avoided in people in whom severe hypoglycaemia can be fatal, such as those with coronary artery disease. Concomitant use of sulfonylureas with intensified insulin regimens should generally be avoided. People should be educated regarding the recognition and management of hypoglycaemia. Weight gain is another undesirable effect of sulfonylureas and is attributed to the anabolic effects of insulin. On the other hand, the drugs are relatively inexpensive and remain a reasonable choice when cost is the primary consideration in treatment decisions [3].

Evaluation of cardiovascular safety for newly approved anti-diabetes agents has become a regulatory requirement since 2008 [14], but large-scale cardiovascular outcomes trials have not been mandated for older agents, including metformin and sulfonylureas. Observational studies and randomized controlled trials comparing second-generation sulfonylureas against various anti-diabetes agents suggest the possibility of an increased risk for cardiovascular events relative to metformin, which might be secondary to potential cardioprotection with metformin [15]. However, dedicated cardiovascular outcomes trials comparing mostly glimepiride either with pioglitazone or the DPP-4 inhibitor linagliptin did not identify a detrimental effect [16, 17].

Meglitinides

Meglitinides (or glinides) including nateglinide and repaglinide are secretagogues that have a similar mechanism of action to sulfonylureas, although they act via different pancreatic β-cell receptors. They have a rapid onset but short duration of action, thereby controlling post-prandial glucose excursions. These agents need frequent dosing and might be considered in people with erratic meal schedules. Meglitinides have a similar risk for weight gain as sulfonylureas, but possibly a lower risk for hypoglycaemia. Repaglinide is principally metabolized by the liver and can be used safely in people with mild to moderate renal impairment, although meglitinides should be titrated slowly based on blood glucose levels to minimize the risk of hypoglycaemia [18].

Pioglitazone

Pioglitazone belongs to the thiazolidinediones class, also known as glitazones, which act by activating peroxisome proliferator-activated receptors (PPAR), especially PPAR-γ [19]. These nuclear receptors are expressed predominantly in adipocytes and skeletal muscles and regulate the transcription of specific genes involved in glucose and lipid metabolism. As a result of PPAR-γ activation, cells become more dependent on the oxidation of glucose to yield energy for cellular processes. Pioglitazone has a delayed onset of action, but provides durable reduction in HbA_{1c} and could offer an advantage in certain clinical settings, such as individuals with severe insulin resistance or non-alcoholic steatohepatitis (NASH) [20]. It does not cause hypoglycaemia, but is associated with weight gain as well as fluid retention due to increased sodium reabsorption in the collecting tubules, especially if used concomitantly with insulin [20]. Consequently, the drug may precipitate or worsen heart failure. In addition, pioglitazone use has been linked to an increased risk of bladder cancer and fractures [21, 22]. Finally, pioglitazone may decrease the incidence of cardiovascular events [23–25].

α-glucosidase inhibitors

α-Glucosidase inhibitors (acarbose, miglitol, voglibose) inhibit the absorption of carbohydrates from the small intestine. They modestly decrease HbA_{1c} [26], but can be useful for reducing post-prandial hyperglycaemia [27]. Since α-glucosidase inhibitors prevent the degradation of complex carbohydrates into glucose, some carbohydrates will remain in the intestine and be delivered to the colon, causing gastrointestinal side effects such as flatulence and diarrhoea. As such, α-glucosidase inhibitors are contraindicated in individuals who have chronic intestinal diseases and in those who have conditions that may deteriorate as a result of increased gas formation in the intestine [27]. Moreover, hypoglycaemia in people treated with these agents can only be effectively improved with the ingestion of glucose. Acarbose is the most commonly used drug of this class, and also the most widely studied. In particular, in the Study to Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM) trial, acarbose significantly increased reversion of impaired glucose tolerance (IGT) to normal glucose tolerance and was associated with a 49% relative risk reduction in the development of cardiovascular events [28, 29]. The Acarbose Cardiovascular Evaluation (ACE) trial, however, which randomized 6522 people with coronary heart disease and IGT to acarbose or placebo and had a follow-up of a median of five years, showed no reduction in the risk of major cardiovascular events with acarbose, although progression to diabetes was reduced [30].

Dipeptidyl-peptidase 4 inhibitors

DPP-4 inhibitors, also referred to as gliptins, are a class of oral anti-diabetes agents that target the enzyme DPP-4, which deactivates endogenous incretins including GIP and GLP-1. Incretins are gut-derived hormones that stimulate glucose-dependent insulin release from the pancreatic islets while suppressing glucagon secretion, and are responsible for the incretin effect, defined as an enhanced insulin secretion following oral glucose administration compared with an isoglycaemic intravenous challenge [31]. In people with type 2 diabetes the incretin effect is substantially reduced or even lost.

DPP-4 inhibitors have a modest effect on lowering blood glucose and a neutral effect on body weight, but carry a minimal risk for hypoglycaemia in the absence of therapies that may otherwise cause hypoglycaemia [6, 32]. They can be used as add-on therapy to metformin or as monotherapy in people with type 2 diabetes for whom metformin is not well tolerated or is contraindicated. Licensed DPP-4 inhibitors across Europe and the USA include alogliptin, linagliptin, saxagliptin, and sitagliptin. Vildagliptin is licensed in Europe but has not received marketing authorization by the US Food and Drug Administration (FDA). The dose of DPP-4 inhibitors should be adjusted based on renal function, with the exception of linagliptin, which is primarily eliminated via the enterohepatic system and can therefore be used in people with end-stage kidney disease.

DPP-4 inhibitors were historically the first anti-diabetes agents evaluated in the context of dedicated cardiovascular outcomes imposed by drug regulators [14]. These trials recruited people at high cardiovascular risk and showed that DPP-4 inhibitors do not increase the risk for major cardiovascular events, including non-fatal myocardial infarction, stroke, and cardiovascular death [33–37]. Nevertheless, an increased risk of hospitalization from worsening heart failure was observed following treatment with saxagliptin.

DPP-4 inhibitors are generally well tolerated. An increased risk of pancreatic adverse events including acute pancreatitis and pancreatic cancer was initially postulated among people treated with incretin mimetics, based primarily on data from post-marketing surveillance systems and animal studies, which suggested higher rates of pancreatic intraepithelial neoplasia with incretin therapies. However, these safety signals have been subsequently alleviated [38]. A potential association of DPP-4 inhibitors with respiratory and urinary tract infections has also been reported. The association of DPP-4 inhibitors with infections has been largely refuted, although it remains questionable whether cases of nasopharyngitis are more common with sitagliptin [39]. Other adverse effects with DPP-4 inhibitors include elevated liver enzymes, skin lesions, inflammatory bowel disease, and joint pain [40]. The favourable safety profile of DPP-4 inhibitors taken together with their modest effect on glycaemia suggests that these agents might be an attractive treatment option for frail individuals in whom intensive glycaemic management and ensuing harms should be avoided.

Glucagon-like peptide 1 receptor agonists

GLP-1 is an incretin produced by the enteroendocrine L cells that enhances peripheral insulin action, slows gastric emptying, and inhibits glucagon secretion. Endogenous GLP-1 has a short half-life and is rapidly deactivated by DPP-4. As such, pharmaceutical efforts have led to the development of synthetic, degradation-resistant GLP-1RAs with favourable pharmacokinetic properties. The first licensed GLP-1RA was exenatide, a synthetic exendin-4 that was discovered in lizard saliva [31]. Licensed GLP-1RAs also include liraglutide and lixisenatide, which are administered once daily by subcutaneous injection, as well as dulaglutide, exenatide extended release, and semaglutide, which are administered once weekly. An oral formulation of semaglutide administered once daily has also received marketing authorization.

GLP-1RAs are effective in improving glycaemic levels, although intraclass variations are noted. Subcutaneous semaglutide is probably the most potent agent in terms of HbA_{1c} lowering, whereas shorter-acting agents such as lixisenatide exhibit less pronounced glycaemic benefits [26]. Because the effects of GLP-1RAs on insulin secretion are glucose dependent, while the counter-regulatory release of glucagon in response to low blood glucose is fully preserved, the risk of hypoglycaemia is minimal. However, dose adjustments of other anti-diabetes medications known to cause hypoglycaemia, such as insulin, sulfonylureas, or meglitinides, might be necessary on initiation of GLP-1RAs. Weight loss is a further advantage of therapy with GLP-1RAs. Besides slowing gastric emptying, thereby inducing nausea and vomiting as side effects, it has been proposed that GLP-1RAs promote satiety by directly acting on appetite centres in the hypothalamus. Of note is that liraglutide 3.0 mg daily and semaglutide 2.4 mg once weekly have received marketing authorization for weight management as an adjunct to a reduced-calorie diet and increased physical activity for adults with obesity (body mass index [BMI] $\geq 30\,kg/m^2$) or overweight (BMI $\geq 27\,kg/m^2$) with at least one comorbidity irrespective of the presence of type 2 diabetes.

Cardiovascular outcomes trials have shown that dulaglutide, liraglutide, and subcutaneous semaglutide reduce the composite cardiovascular endpoint of non-fatal myocardial infarction, stroke, and cardiovascular death [41–43]. Oral semaglutide reduced cardiovascular death [44], whereas exenatide extended release and lixisenatide had a neutral effect on cardiovascular endpoints [45, 46]. Moreover, dulaglutide and subcutaneous semaglutide decreased incidence of stroke, while extended-release exenatide, liraglutide, and oral semaglutide reduced all-cause mortality [26]. The cardiovascular benefits of GLP-1RAs cannot be attributed to improved glycaemic levels alone and might be related to effects on other important risk factors such as body weight, blood pressure, and cholesterol profile [6]. Emerging evidence suggests that these drugs might independently attenuate the progression of atherosclerosis. Based on the aforementioned findings, GLP-1RAs are now recommended in people with type 2 diabetes and established cardiovascular disease or multiple cardiovascular risk factors [1]. This recommendation is not contingent on HbA_{1c}, in recognition of the glucose-independent cardiovascular benefits of these agents [1, 2]. These recommendations are also reflected in the revised labelling of dulaglutide, liraglutide, and subcutaneous semaglutide, for which the indication has been expanded beyond glycaemic management to include the reduction of major cardiovascular events.

GLP-1RAs are generally effective and safe in people with declining kidney function. Dulaglutide, liraglutide, and semaglutide can be used without dose adjustments, even in severe renal impairment for which treatment options beyond insulin therapy are limited. Based on data from cardiovascular outcomes trials, GLP-1RAs ameliorate the progression of albuminuria, although no long-term benefit was observed with respect to decline in eGFR [47].

The main side effects of therapy with GLP-1RAs are nausea and to some extent vomiting and diarrhoea, which are related to slowing of gastric emptying. These symptoms are dose dependent and usually wane during the course of treatment. Slow dose escalation to minimize these side effects is suggested. GLP-1RAs should be avoided in people with gastroparesis. Local site reactions appear more common with GLP-1RAs compared with insulin injections. Similar to DPP-4 inhibitors, early concerns about an increased risk of acute pancreatitis or pancreatic cancer have largely abated [38]. Animal studies have also suggested a potential association of certain GLP-1RAs with thyroid C-cell neoplasms and as a precaution these agents should be avoided in people with a history of medullary cancer or multiple endocrine neoplasia 2. GLP-1RAs could possibly increase risk for gallbladder adverse events including acute cholecystitis [42], although it remains unclear whether these side effects are caused by

rapid weight loss or other underlying mechanisms. Finally, an increased incidence of diabetic retinopathy complications was observed with subcutaneous semaglutide, but it is unclear whether this effect was mediated by a rapid decline of HbA_{1c} [43]. Therefore, frequent retinal screening to detect progression of retinopathy might be prudent for individuals treated with semaglutide.

Sodium–glucose cotransporter 2 inhibitors

SGLT-2 is expressed in the proximal convoluted tubule and is responsible for the reabsorption of ~90% of the filtered glucose load. SGLT-2 inhibitors, also called gliflozins, are a recent addition to the therapeutic armamentarium for type 2 diabetes. They lead to increased urinary glucose excretion, thereby lowering plasma glucose levels. Because of this insulin-independent mode of action, SGLT-2 inhibitors do not increase the risk of hypoglycaemia. Nevertheless, the glycaemic efficacy of SGLT-2 inhibitors is relatively modest and limited by any decline in renal function. Other benefits include weight loss and modest blood pressure reduction as a result of osmotic diuresis [48]. Currently, four SGLT-2 inhibitors have been approved by regulatory authorities in Europe and the USA, namely canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin.

The SGLT-2 inhibitor cardiovascular outcomes trials have changed the landscape in the management of type 2 diabetes [49–52]. Empagliflozin and canagliflozin reduced major cardiovascular events, whereas empagliflozin also showed a benefit for all-cause mortality. The cardiovascular benefits of SGLT-2 inhibitors generally occur early in the course of treatment and are probably multidimensional in nature. The underlying mechanisms could involve glycaemic levels, weight loss, blood pressure reduction, lowering of uric acid levels, or changes in arterial stiffness. All SGLT-2 inhibitors consistently lowered hospitalizations for heart failure, an observation that can partly be explained by natriuresis. Risk reduction of worsening heart failure is a class effect that has been corroborated in people who received empagliflozin or dapagliflozin even in the absence of type 2 diabetes [53–55]. As such, dapagliflozin and empagliflozin are now indicated for chronic heart failure.

SGLT-2 inhibitors also reduce the risk of end-stage kidney disease [56–58]. The FDA has updated the indications for most SGLT-2 inhibitors to reflect cardiorenal protection. The drugs stabilize kidney function and alleviate the progression of albuminuria, possibly through activation of tubuloglomerular feedback, which leads to a reduction of intraglomerular pressure and prevents hyperfiltration. Initiation of SGLT-2 inhibitors is associated with a temporary decrease in eGFR, which stabilizes over time, a pattern that is also observed with renin–angiotensin system blockade. Assessment of renal function is recommended before initiation of SGLT-2 inhibitors and periodically thereafter (at least yearly). Dose adjustments are necessary for canagliflozin and empagliflozin in people with moderate renal impairment (eGFR <60 ml/min/1.73 m^2).

The most common adverse effects of therapy with SGLT-2 inhibitors are genital mycotic infections, which are related to glucosuria and include mainly cases of balanoposthitis in men and vulvovaginal candidiasis in women. They are generally of mild to moderate intensity, respond well to standard therapy, and do not tend to reoccur. Urinary tract infections are less common and reports of pyelonephritis, urosepsis, or Fournier's gangrene are extremely rare. A numerical imbalance of bladder cancer cases was also noted in the clinical development programme of dapagliflozin, but early detection after short exposure and potential detection bias due to frequent urinalysis point against causality. Volume depletion–related adverse events including dizziness, orthostatic hypotension, and syncope may also be precipitated by SGLT-2 inhibitors in older individuals, people with renal impairment, and in cases of concomitant therapy with thiazides or loop diuretics. The risk of acute kidney injury does not appear to be increased. Thrombosis due to haemoconcentration is another theoretical concern. The incidence of fractures was higher among those taking canagliflozin, but was likely related to falls resulting from volume depletion. For canagliflozin an increased risk of amputations was also reported and, as such, consideration may be given to stopping treatment in people who develop events that may precede amputation, such as lower-extremity skin ulcer, infection, osteomyelitis, or gangrene [26,48]. Finally, people treated with SGLT-2 inhibitors might be prone to the development of diabetic euglycaemic ketoacidosis in the setting of intercurrent illness [59]. In these individuals the absence of marked hyperglycaemia might delay the recognition and treatment of this rare complication. People should be advised to withhold treatment with SGLT-2 inhibitors during acute illness or in the perioperative period, and the drugs should be avoided in people predisposed to diabetic ketoacidosis (e.g. pancreatic insufficiency or alcohol abuse).

Dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide 1 receptor agonists

Combined GLP-1 and GIP receptor activation has also been examined as a promising therapeutic option, based on the rationale that the two incretins can have synergistic and complementary actions [60]. Tirzepatide is the first dual GIP and GLP-1 receptor agonist that has received marketing approval by the FDA for the treatment of type 2 diabetes. It has greater affinity to the GIP, rather than GLP-1, receptor and is administered subcutaneously once weekly. Meta-analysis has shown that tirzepatide is more efficacious in lowering HbA_{1c} than once-weekly GLP-1RAs (semaglutide and dulaglutide) and basal insulin analogues [61]. Treatment with tirzepatide also induced greater body weight reduction compared with GLP-1RAs, but was associated with an increased incidence of gastrointestinal adverse events, mostly nausea [61]. Limited cardiovascular data, derived mostly from one trial, suggest that tirzepatide does not increase the risk of major cardiovascular events [62].

Insulin

Due to the progressive nature of the disease, many people with type 2 diabetes will eventually require insulin therapy. Insulin might also be the sole therapeutic option for certain populations such as people with advanced kidney disease or cirrhosis. Insulin has theoretically unlimited efficacy with respect to HbA_{1c} lowering that is constrained only by the development of hypoglycaemia. However, insulin therapy is associated with weight gain and requires considerable self-management skills and adequate support, because of the need for more frequent blood glucose monitoring and dose adjustment. People should also receive training in the recognition and management of hypoglycaemic episodes.

Human insulin has largely been replaced by insulin analogues, which are produced by modifications to the amino acid sequence of insulin that alter its pharmacokinetic properties (Chapter 31). The following formulations of insulin are available in the USA or Europe:

- Human insulins:
  - Short-acting regular insulin.
  - Concentrated regular insulin U-500.
  - Intermediate acting neutral protamine Hagedorn (NPH), also called isophane insulin.
  - Premixed combinations of these.

- Basal insulin analogues:
  - Insulin glargine U-100 and biosimilars.
  - Insulin detemir.
  - Ultra-long-acting insulin degludec.
  - Concentrated forms of insulin glargine U-300 and insulin degludec U-200.
- Prandial insulin analogues:
  - Short- and rapid-acting insulins aspart, glulisine, and lispro.
  - Faster-acting insulin aspart.
  - Ultra-rapid lispro.
- Premixed basal/prandial regimens.

Basal insulin is meant to cover the basic metabolic requirements, whereas prandial insulin regulates mealtime glucose excursions. People with type 2 diabetes progressing to insulin therapy usually start with once-daily bedtime administration of basal insulin, although NPH and insulin detemir may also be dosed twice daily. The starting dose of basal insulin is 10 units or 0.1–0.2 units/kg and titration is based on fasting glucose levels. The differences in glycaemic efficacy among basal insulin analogues are likely minimal and of limited clinical significance. Newer agents including insulin degludec and glargine U300 have longer duration of action and lower rates of nocturnal hypoglycaemia, whereas insulin detemir might have a more favourable profile with respect to weight gain [63]. Concentrated preparations such as degludec U-200 and glargine U-300 allow injection of a reduced volume and might be more convenient for people with higher requirements because of insulin resistance. Basal insulin analogues are considerably more costly than NPH, although cheaper biosimilars have become available. Finally, data from cardiovascular safety trials are reassuring for insulin glargine and degludec [64, 65].

Once basal insulin dose has exceeded 0.5 units/kg or if the fasting glucose target is met but the desired HbA_{1c} target has not been achieved, insulin therapy should be intensified by adding doses of prandial to basal insulin. A starting dose of 4 units or 0.1 units/kg of prandial insulin (or 10% of the amount of basal insulin) is initially administered at the largest meal of the day. Dose can be gradually increased by 1–2 units or 10–15% to meet post-prandial glucose targets. If the HbA_{1c} is still above target, this basal-plus scheme can then be advanced to a basal-bolus regimen with the stepwise addition of mealtime insulin injections. During this process decreasing doses of basal insulin might be required to avoid hypoglycaemia. Regular human insulin should be administered ~30 minutes before start of the meal to match post-prandial glucose excursions. The rapid-acting insulin analogues aspart, glulisine, and lispro have an onset of action within 15 minutes of injection and quicker return to baseline concentrations. Finally, the newly approved faster-acting insulin aspart and ultra-rapid lispro have accelerated absorption and even earlier onset of action, but also earlier offset of exposure. In this regard, they resemble more closely physiological mealtime insulin secretion and could therefore offer better post-prandial glucose regulation while minimizing the risk of post-prandial hypoglycaemia [66].

Alternatively, for individuals using basal insulin for whom prandial coverage is required, the regimen can be converted to two doses of premixed basal/prandial insulin by splitting the total insulin dose. Premixed regimens might be more practical for people with frailty for whom tight glycaemic levels are not desirable, whereas basal-bolus regimens allow greater flexibility for people with irregular eating habits [3].

Clinicians and people with diabetes sometimes are reluctant to start insulin, which may delay timely intensification of therapy (therapeutic inertia). People with diabetes might find it difficult to accept insulin therapy because of fear of injections, life restrictions, or risk of hypoglycaemia. Moreover, starting insulin therapy could be felt as a personal failure in the management of the disease. Healthcare providers should address these misconceptions during the clinical encounter and avoid using insulin therapy as a threat to motivate people [67]. Notably, modern, prefilled pen devices have appreciably simplified insulin administration.

Rationale for treatment selection

Glycaemic management

Management of hyperglycaemia has traditionally guided the initiation and escalation of glucose-lowering therapy in people with type 2 diabetes. Indeed, landmark trials have corroborated the beneficial effects of tight glycaemic levels, mainly for the reduction of microvascular complications. In contrast, the impact of intensive glucose lowering on incident macrovascular events is less certain [8, 68, 69]. Measurement of HbA_{1c} remains the primary tool for assessment of glycaemia. The test reflects average glucose levels over ~3 months and is strongly predictive of diabetes-related complications. Observational studies suggest that each 1% (11 mmol/mol) reduction in HbA_{1c} is associated with risk reductions of 37% for microvascular complications, 14% for myocardial infarction, and 21% for diabetes-related mortality [70]. Nevertheless, as HbA_{1c} decreases, a U-shaped relationship with all-cause mortality and cardiac events is observed [71], especially in older individuals and people with frailty or established cardiovascular disease, for whom hypoglycaemia is a limiting factor for intensifying treatment. The HbA_{1c} target for most people with type 2 diabetes is <7% (53 mmol/mol), but it may be lower for well-motivated individuals, while higher HbA_{1c} goals such as <8% (64 mmol/mol) might be more appropriate for people with limited life expectancy [72]. If prevention of hypoglycaemia is a therapeutic priority, the use of sulfonylureas or insulin is discouraged. The vast majority of studies for medications for type 2 diabetes have utilized HbA_{1c} as the primary outcome measure for glycaemic efficacy. Anti-diabetes drugs have variable glucose-lowering effects, with insulin regimens and specific GLP-1RAs producing the greatest HbA_{1c} reduction [26]. The newly approved dual GIP/GLP-1 receptor agonist tirzepatide offers an even more pronounced HbA_{1c} reduction, as high as 2% (22 mmol/mol) [61].

The standard approach to glycaemic management has been to initiate metformin monotherapy followed by the stepwise addition of anti-diabetes agents until the individualized HbA_{1c} target is reached. The Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of type 2 diabetes (VERIFY) trial showed that upfront combination therapy with metformin plus a DPP-4 inhibitor improves the durability of the glycaemic effect compared with sequential addition of anti-diabetes drugs [73]. Combination therapy can target multiple physiological derangements simultaneously and could also decrease medication burden and improve medication taking. GLP-1RAs are considered first-line injectable therapy in type 2 diabetes and should be prioritized over basal insulin, because they have comparable glycaemic efficacy, induce weight loss, and confer a low risk of hypoglycaemia [74]. For people with catabolic symptoms including weight loss, hypertriglyceridaemia, and ketosis or severe hyperglycaemia (i.e. HbA_{1c} >10% [86 mmol/mol] or blood glucose levels ≥300 mg/dl [16.7 mmol/l]), introduction of insulin should be considered. After resolution of glucose

toxicity, the therapeutic regimen may be simplified [1]. Fixed ratio combinations of GLP-1RAs with basal insulin allowing co-administration through a single injection are also commercially available. These co-formulations provide further improvements in glycaemia while balancing out weight gain and risk of hypoglycaemia [75].

The HbA_{1c} test has limitations, as it does not capture hypoglycaemic episodes or glucose variability and results might be unreliable under circumstances that alter red blood cell turnover (anaemia, haemoglobinopathies, or end-stage renal disease with erythropoietin therapy). In these situations, capillary glucose measurements may supplement treatment decisions. Beyond people receiving insulin therapy for whom frequent measurements are required for dose titration, self-monitoring of blood glucose has limited clinical value in terms of glycaemic management and is associated with higher treatment cost without evidently improving quality of life [76]. In recent years, continuous glucose monitoring (CGM) has been fully incorporated into the management of type 1 diabetes, although evidence supporting its use in type 2 diabetes remains limited. Time in range (TIR) and the glucose management indicator (GMI) derived from CGM are useful metrics of glucose levels that correlate well with HbA_{1c}. The ambulatory glucose profile (AGP), which includes time below and above target range, can be used to develop a more personalized treatment plan, especially for people receiving insulin therapy [77]. Remote access to CGM data will also potentially transform healthcare encounters. In the near future, it is expected that more trials in type 2 diabetes will evaluate the effect of anti-diabetes agents on TIR instead of HbA_{1c} as the primary glycaemic endpoint.

Management for prevention of complications

Evidence from cardiovascular outcomes trials

In the past, regulatory bodies approved new medications for diabetes solely on the basis of their glucose-lowering potential, even though it was recognized that regulation of hyperglycaemia is a surrogate for reducing the microvascular, and to a lesser extent the macrovascular, complications of diabetes. Evidence on the potential benefit of glucose-lowering drugs on specific cardiovascular outcomes first became available for metformin in a substudy of the UKPDS; UKPDS 34 was a randomized controlled trial that assessed whether intensive treatment with metformin reduced the risk of diabetes-related complications compared to conventional treatment policy (diet alone) in 753 individuals with overweight and newly diagnosed type 2 diabetes [7]. After a median follow-up of 10.7 years, participants allocated to metformin had risk reductions of 32% for any diabetes-related endpoint (a composite of mortality and vascular outcomes) and 36% for all-cause mortality [7].

Following a similar rationale to that of the UKPDS, and also based on trial data suggesting a beneficial effect of thiazolidinediones on multiple cardiovascular risk factors, the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) and the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) studies evaluated the cardiovascular effects of pioglitazone and rosiglitazone, respectively [23,78]. The PROactive study (5238 participants) found that, over an average period of 34.5 months, pioglitazone reduced the composite of all-cause mortality, or myocardial infarction, or stroke versus placebo (hazard ratio [HR] 0.84; 95% confidence interval [CI] 0.72 to 0.98). However, the effect of pioglitazone on the primary outcome (composite of all-cause mortality, non-fatal myocardial infarction including silent myocardial infarction, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle) was not significant [23]. The RECORD trial (4447 participants) found that rosiglitazone in combination with metformin or sulfonylurea was non-inferior to metformin and sulfonylurea dual therapy in terms of the composite outcome of cardiovascular death, myocardial infarction, or stroke (three-component major adverse cardiovascular events, MACE) [78]. Notably, in both trials thiazolidinediones considerably increased the risk of heart failure compared to control.

In 2008 the FDA, and later the European Medicines Agency, required that a dedicated cardiovascular outcomes trial be conducted as a prerequisite for the regulatory approval of new anti-diabetes drugs [14]. This change in policy was probably influenced by an earlier FDA decision to reject the approval of muraglitazar following the publication of a relevant meta-analysis of cardiovascular outcomes [79], but was mainly triggered by the findings of a meta-analysis for rosiglitazone [4]. This meta-analysis suggested that rosiglitazone, which was widely used in the USA and Europe at that time, increased the risk of myocardial infarction compared to placebo and other anti-diabetes regimens [4]. Subsequently, several cardiovascular outcomes trials have been completed, mainly for DPP-4 inhibitors, GLP-1RAs, and SGLT-2 inhibitors.

To achieve feasible and adequate power, cardiovascular outcomes trials typically have assessed the composite endpoint of MACE as primary outcome and have recruited people with type 2 diabetes and increased cardiovascular risk, defined as history of atherosclerotic disease or presence of multiple cardiovascular risk factors. The main findings of cardiovascular outcomes trials in type 2 diabetes for anti-diabetes drugs approved in the USA or Europe are presented in Table 37.2. In summary, trials of DPP-4 inhibitors have demonstrated a neutral effect on cardiovascular outcomes. Similarly, in the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial, insulin glargine had a neutral effect on cardiovascular outcomes [64], while in the Trial comparing cardiovascular safety of insulin degludec versus insulin glargine in subjects with type 2 diabetes at high risk of cardiovascular events (DEVOTE), insulin degludec was non-inferior to insulin glargine with respect to major cardiovascular events [65]. Notable favourable effects on MACE and mortality outcomes were evident in cardiovascular outcomes trials of specific GLP-1RAs and SGLT-2 inhibitors. Moreover, both drug classes have demonstrated benefits in kidney outcomes, while SGLT-2 inhibitors also improved heart failure endpoints. Consequently, the effect of specific SGLT-2 inhibitors on these outcomes has also been assessed in dedicated trials focusing on people with chronic kidney disease or heart failure irrespective of history of diabetes. As such, current guidance in the pharmacological management of type 2 diabetes advocates that choice of therapeutic options should be primarily based on atherosclerotic cardiovascular risk profile and presence of chronic kidney disease, heart failure, or obesity-related morbidities [1,80].

Among cardiovascular outcomes trials with GLP-1RAs, the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial was the first to be reported. Over a median follow-up of 24 months, ELIXA compared once-daily lixisenatide (at a maximum daily dose of 20 μg) with placebo in 6068 people with type 2 diabetes and a recent (within 180 days) acute coronary event [46]. Lixisenatide was non-inferior, but not superior, to placebo for the primary composite endpoint of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina (four-component MACE), with an HR of 1.02 (95% CI 0.89 to 1.17) [46].

Table 37.2 Findings from major cardiovascular outcome trials for pharmaceutical agents approved for the treatment of type 2 diabetes in Europe or the USA.

Anti-diabetes agent	Trial[a]	Major adverse cardiovascular events[b]	Hospitalization for heart failure	All-cause mortality
Pioglitazone	PROACTIVE [23]	0.82 (0.70 to 0.97)	1.41 (1.10 to 1.80)	0.96 (0.78 to 1.18)
	TOSCA.IT [16]	0.96 (0.74 to 1.26)	1.57 (0.76 to 3.24)	1.08 (0.71 to 1.65)
DPP-4 inhibitors				
Alogliptin	EXAMINE [33,34]	0.96 (≤1.16)[c]	1.07 (0.79 to 1.46)	0.88 (0.71 to 1.09)
Linagliptin	CARMELINA [35]	1.02 (0.89 to 1.17)	0.90 (0.74 to 1.08)	0.98 (0.84 to 1.13)
	CAROLINA [17]	0.98 (0.84 to 1.14)	1.00 (0.84 to 1.20)	0.91 (0.78 to 1.06)
Saxagliptin	SAVOR-TIMI 53 [36]	1.00 (0.89 to 1.12)	1.27 (1.07 to 1.51)	1.11 (0.96 to 1.27)
Sitagliptin	TECOS [37]	0.99 (0.89 to 1.10)	1.00 (0.83 to 1.20)	1.01 (0.90 to 1.14)
GLP-1 receptor agonists				
Dulaglutide	REWIND [41]	0.88 (0.79 to 0.99)	0.93 (0.77 to 1.12)	0.90 (0.90 to 1.01)
Exenatide LAR	EXSCEL [45]	0.91 (0.89 to 1.00)	0.94 (0.78 to 1.13)	0.86 (0.77 to 0.97)
Lixisenatide	ELIXA [46]	1.02 (0.89 to 1.17)	0.96 (0.75 to 1.23)	0.94 (0.78 to 1.13)
Liraglutide	LEADER [42]	0.87 (0.78 to 0.97)	0.87 (0.73 to 1.05)	0.85 (0.74 to 0.97)
Subcutaneous semaglutide	SUSTAIN-6 [43]	0.74 (0.58 to 0.95)	1.11 (0.77 to 1.61)	1.05 (0.74 to 1.50)
Oral semaglutide	PIONEER 6 [44]	0.79 (0.57 to 1.11)	0.86 (0.48 to 1.55)	0.51 (0.31 to 0.84)
SGLT-2 inhibitors				
Canagliflozin	CANVAS PROGRAM [49]	0.86 (0.75 to 0.97)	0.67 (0.52 to 0.87)	0.87 (0.74 to 1.01)
Dapagliflozin	DECLARE-TIMI 58 [51]	0.93 (0.84 to 1.03)	0.73 (0.61 to 0.88)	0.93 (0.82 to 1.04)
Empagliflozin	EMPA-REG OUTCOME [52]	0.86 (0.74 to 0.99)	0.65 (0.50 to 0.85)	0.68 (0.57 to 0.82)
Ertugliflozin	VERTIS CV [50]	0.97 (0.85 to 1.11)	0.70 (0.54 to 0.90)	0.93 (0.80 to 1.08)
Basal insulin analogues				
Degludec	DEVOTE [65]	0.91 (0.78 to 1.06)	0.88 (0.72 to 1.08)	0.91 (0.76 to 1.11)
Glargine U-100	ORIGIN [64]	1.02 (0.94 to 1.11)	0.90 (0.77 to 1.05)	0.98 (0.90 to 1.08)

Results are expressed as hazard ratios and 95% confidence intervals. Green indicates a favourable effect, yellow indicates a neutral effect, and red indicates a detrimental effect. DPP-4, dipeptidyl-peptidase 4; GLP-1, glucagon-like peptide 1; LAR, long-acting release; SGLT-2, sodium-glucose cotransporter 2.

[a] Comparisons against placebo except for the TOSCA-IT trial, in which pioglitazone was compared with sulfonylureas; the CAROLINA trial, in which linagliptin was compared with glimepiride; and the DEVOTE trial, in which insulin degludec was compared with glargine U-100.

[b] Composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (including also urgent coronary revascularization in the TOSCA.IT trial for pioglitazone and hospitalization for unstable angina in the ELIXA trial for lixisenatide).

[c] Upper boundary of the one-side repeated confidence interval.

In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, 9340 participants with type 2 diabetes were randomized to either once-daily 1.8 mg (or the maximum tolerated dose) liraglutide or placebo in addition to their standard care and were followed over a median of 3.8 years [42]. All participants were at increased cardiovascular risk, defined as either an age of more than 50 years with a history of a cardiovascular condition (coronary heart disease, cerebrovascular disease, peripheral vascular disease, chronic kidney disease, or heart failure) or an age of more than 60 years with at least one cardiovascular risk factor (including microalbuminuria, hypertension, left ventricular dysfunction, or an ankle-brachial index of less than 0.9). Most participants (81.3%) had established cardiovascular disease, chronic kidney disease of stage 3 or higher, or both. Treatment with liraglutide reduced the incidence of the primary outcome of first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (three-component MACE) with an HR of 0.87 (95% CI 0.78 to 0.97). This effect was mainly driven by a reduction in cardiovascular mortality (HR 0.78; 95% CI 0.66 to 0.93), whereas the effects on non-fatal myocardial infarction and on non-fatal stroke did not significantly differ between liraglutide and placebo. Treatment with liraglutide also reduced the incidence of all-cause mortality (HR 0.85; 95% CI 0.74 to 0.97) and of the composite kidney outcome (HR 0.78; 95% CI 0.67 to 0.92), the latter being primarily driven by the effect on new-onset macroalbuminuria [42,81].

The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) assessed the cardiovascular effects of once-weekly exenatide versus placebo in 14 752 people with type 2 diabetes over a median of 3.2 years [45]. As per the trial design, ~70% of enrolled participants had a previous cardiovascular event prior to randomization, defined as a history of major clinical manifestation of coronary artery disease, ischaemic cerebrovascular disease, or atherosclerotic peripheral artery disease. The primary outcome of three-component MACE occurred in fewer participants in the exenatide arm

compared with the placebo arm, yielding a marginally non-significant HR of 0.91 (95% CI 0.83 to 1.00). Incidence of all-cause mortality was lower in the exenatide arm (HR 0.86; 95% CI 0.77 to 0.97); however, this effect was not deemed significant on the basis of the hierarchical testing plan that was implemented [45].

The cardiovascular profile of once-weekly subcutaneous semaglutide was evaluated in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), in which 3297 participants were randomized in a 1 : 1 : 1 : 1 ratio to semaglutide 0.5 mg, or 1 mg, or two volume-matched placebo arms [43]. The eligibility criteria regarding participants' cardiovascular risk profile at baseline were identical to those in the LEADER trial [42], and the percentage of enrolled individuals with established vascular disease (83%) was also similar to the LEADER trial. SUSTAIN-6 was not event driven but had a predefined 104-week treatment period. Both doses of semaglutide were superior to placebo in reducing the three-component MACE (HR 0.74; 95% CI 0.58 to 0.95) and the outcome of new or worsening nephropathy comprising macroalbuminuria, doubling of serum creatinine, or the need for renal-replacement therapy (HR 0.64; 95% CI 0.46 to 0.88). However, diabetic retinopathy complications were more frequent with semaglutide in comparison to placebo (HR 1.76; 95% CI 1.11 to 2.78) [43].

The once-daily oral formulation of semaglutide was assessed in the Peptide Innovation for Early Diabetes Treatment (PIONEER 6) trial [44]. Although it was event driven, PIONEER 6 was designed to assess the non-inferiority, and not the superiority, of oral semaglutide versus placebo. It followed 3183 participants over a median of 15.9 months, 2695 (84.7%) of whom had established cardiovascular disease or chronic kidney disease, while the remainder had cardiovascular risk factors only. The primary outcome of MACE occurred in 3.8% of participants receiving semaglutide (at a target daily dose of 14 mg) and in 4.8% of participants allocated to placebo, thus confirming the non-inferiority of oral semaglutide compared with placebo. Treatment with oral semaglutide was also associated with reduced all-cause mortality (HR 0.51; 95% CI 0.31 to 0.84) and cardiovascular mortality (HR 0.49; 95% CI 0.27 to 0.92); however, the trial was neither designed nor adequately powered to assess the superiority of semaglutide over placebo on any of these outcomes [44].

The effect of once-weekly dulaglutide on cardiovascular endpoints was assessed in the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial [41]. As opposed to the other cardiovascular outcomes trials with GLP-1RAs, only 31.5% of the 9091 participants in the REWIND trial had previous cardiovascular disease. The remainder were either older than 60 years with at least two risk factors (tobacco use, dyslipidaemia, hypertension, or obesity) or older than 55 years with myocardial ischaemia, coronary, carotid, or lower-extremity stenosis exceeding 50%, left ventricular hypertrophy, eGFR <60 ml/min/1.73 m^2, or albuminuria. During a median follow-up of 5.4 years, MACE occurred in fewer participants assigned to dulaglutide than those assigned to placebo (HR 0.88; 95% CI 0.79 to 0.99). In terms of individual MACE components, dulaglutide versus placebo significantly reduced non-fatal stroke (HR 0.76; 95% CI 0.61 to 0.95), but not non-fatal myocardial infarction or cardiovascular death [41]. Moreover, dulaglutide was superior to placebo in reducing a composite kidney outcome comprising the development of macroalbuminuria, a sustained 30% or greater decline in eGFR, or renal replacement therapy (HR 0.85; 95% CI 0.77 to 0.93) [41]. As was also the case with the LEADER trial, this effect was mainly driven by the favourable effect on new-onset macroalbuminuria.

Once-weekly albiglutide was compared with placebo in the Harmony Outcomes trial, which included 9463 people with type 2 diabetes and established coronary, cardiovascular, or peripheral artery disease [82]. During a median follow-up of 1.6 years, albiglutide was superior to placebo in reducing MACE (HR 0.78; 95% CI 0.68 to 0.90). Interestingly, albiglutide was the only GLP-1RA that achieved statistical significance versus placebo in terms of reducing the incidence of myocardial infarction (HR 0.75; 95% CI 0.61 to 0.90) [82]. Albiglutide has been withdrawn from the market by the manufacturer in both the USA and Europe for economic reasons.

More recently, the cardiovascular and renal effects of once-weekly efpeglenatide were assessed in the Effect of efpeglenatide on cardiovascular outcomes (AMPLITUDE-O) trial [83]. Of the 4076 participants, ~90% had a history of coronary artery disease, stroke, or peripheral artery disease, while the remaining participants had kidney disease and at least one cardiovascular risk factor. Over a median follow-up of 1.81 years, compared to placebo, efpeglenatide (at a maintenance dose of 4 mg or 6 mg per week) reduced MACE (HR 0.73; 95% CI 0.58 to 0.92) and the composite kidney outcome of macroalbuminuria plus a decrease in kidney function (HR 0.68; 95% CI 0.57 to 0.79). An interesting finding of a subgroup analysis in AMPLITUDE-O was that the beneficial cardiovascular effects of efpeglenatide did not seem to be affected by the concomitant use of an SGLT-2 inhibitor (15% of trial participants) [83]. Efpeglenatide is not available for clinical use.

The dual GIP/GLP-1 receptor agonist tirzepatide was not associated with an increased incidence of MACE with insulin glargine in the Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4) trial over one year of treatment [84]. However, SURPASS-4 was not designed to assess cardiovascular outcomes; the ongoing SURPASS-CVOT trial (NCT04255433) is expected to elucidate the cardiovascular profile of tirzepatide.

A meta-analysis synthesizing data from eight cardiovascular outcomes trials found that GLP-1RAs as a drug class reduced MACE by 14% (HR 0.86; 95% CI 0.80 to 0.93) in comparison to placebo, corresponding to a number needed to treat (NNT) of 65 (95% CI 45 to 130) for a period of three years [85]. Across trials, the point estimate of each individual trial, albeit not always statistically significant, was consistently in favour of the GLP-1RA arm, except for lixisenatide in the ELIXA trial. It has been speculated that this may be partly attributed to the shorter half-life of lixisenatide (2–3 h) than other GLP-1RAs, suggesting that exposure to lixisenatide in ELIXA might have been lower than optimal in view of its once-daily dosing [85]. When ELIXA was excluded from the meta-analysis, heterogeneity was reduced, leading to the certainty of evidence regarding the overall effect of GLP-1RAs on MACE to be classified as high [85] according to Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria [86]. In terms of individual MACE components, meta-analysis results suggested that GLP-1RAs, compared with placebo, significantly reduced the risk of cardiovascular mortality, myocardial infarction, and stroke by 13%, 10%, and 17%, respectively. All-cause mortality was also reduced with GLP-1RAs, with an HR of 0.88 (95% CI 0.82 to 0.94) corresponding to an NNT of 114 (95% CI 76 to 228) for a period of three years. Treatment with a GLP-1RA was associated with an 11% lower risk of hospitalization for heart failure and a 21% lower risk of a broad composite kidney outcome [85]. These findings have been corroborated in an additional

meta-analysis [87]; however, their clinical interpretation should take into consideration that, across GLP-1RA trials, details about heart failure were often incomplete and not standardized, while the effect on the composite kidney outcome was primarily driven by the reduction in the macroalbuminuria component (HR 0.74; 95% CI 0.67 to 0.82) [87].

One question of particular clinical relevance is whether the overall cardiovascular benefits of GLP-1RAs are equally applicable both to people with established atherosclerotic disease and to people with cardiovascular risk factors only. In this regard, the majority of participants in individual cardiovascular outcomes trials had established cardiovascular disease (ranging between 70% and 100%), the only exception being the REWIND trial, in which ~70% of participants had a combination of cardiovascular risk factors but not established vascular disease. An earlier meta-analysis of five trials suggested that the overall beneficial effect of GLP-1RAs on MACE was evident solely in individuals with a history of cardiovascular disease, based on the statistically significant value of the test for interaction between subgroups (P for interaction) [88]. However, subsequent meta-analyses incorporating data from all eight trials found no significant interaction between the two subgroups of people with and without established cardiovascular disease in terms of the overall effect estimate on MACE, even though the subgroup estimate was greater in those with known cardiovascular disease [85, 89]. Nevertheless, the credibility and clinical interpretation of these meta-analyses of subgroups should not be based solely on the value of a statistical test for interaction between subgroups, but additional aspects should also be taken into consideration [90].

Among cardiovascular outcomes trials with SGLT-2 inhibitors, the Empagliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients (EMPA-REG OUTCOME) was the first to be reported. EMPA-REG OUTCOME assessed the effects of empagliflozin (at a dose of either 10 mg or 25 mg) on cardiovascular events versus placebo in 7020 adults with type 2 diabetes and established cardiovascular disease (history of myocardial infarction, stroke, single- or multi-vessel coronary artery disease, or occlusive peripheral artery disease) [52]. Over a median follow-up of 3.1 years, participants who received empagliflozin had a lower rate of the primary outcome of three-component MACE (HR 0.86; 95% CI 0.74 to 0.99), cardiovascular mortality (HR 0.62; 95% CI 0.49 to 0.77), and all-cause mortality (HR 0.68; 95% CI 0.57 to 0.82). Treatment with empagliflozin also reduced hospitalization for heart failure by 35% and the composite kidney outcome of incident or worsening nephropathy by 39% [52, 56]. This beneficial effect was evident in each individual component of the composite kidney outcome, comprising macroalbuminuria, doubling of serum creatinine, and initiation of renal-replacement therapy [56].

The cardiovascular effects of canagliflozin (100 mg or 300 mg) were examined in 10 142 people with type 2 diabetes in the CANVAS Program, which integrated data from the Canagliflozin Cardiovascular Assessment Study (CANVAS) and CANVAS-Renal (CANVAS-R) [49]. CANVAS was designed with the aim of meeting the 2008 FDA cardiovascular safety (non-inferiority) requirements, and as such was insufficient to enable a test of a positive cardiovascular effect (superiority) of canagliflozin over placebo [49]. On this ground, CANVAS-R was undertaken with a similar design to CANVAS to jointly achieve statistical power to detect plausible favourable effects of canagliflozin on cardiovascular and kidney outcomes [91]. Participants' eligibility criteria were identical in both trials, with ~65% of the CANVAS Program population having a history of cardiovascular disease, and the remaining being 50 years or older with two or more cardiovascular risk factors. During a median follow-up of 126 weeks in the overall CANVAS Program, MACE occurred in fewer participants assigned to canagliflozin than those assigned to placebo, with an HR of 0.86 (95% CI 0.75 to 0.97). In addition, fewer participants in the canagliflozin group were hospitalized for heart failure (HR 0.67; 95% CI 0.52 to 0.87) and had the composite kidney outcome of sustained reduction in eGFR, need for renal-replacement therapy, or renal death (HR 0.60; 95% CI 0.47 to 0.77) [49].

In the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial, 17 160 people with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease were randomized to either dapagliflozin 10 mg or placebo and were followed for a median of 4.2 years [51]. A notable characteristic differentiating DECLARE-TIMI 58 from other cardiovascular outcomes trials with SGLT-2 inhibitors was that this trial included more than 10 000 individuals (~60% of the trial population) without evident cardiovascular disease but with multiple risk factors. MACE was originally the sole primary outcome, but the study protocol was amended to include the composite of cardiovascular death or hospitalization of heart failure as a second primary outcome. The rate of MACE was similar between dapagliflozin and placebo (HR 0.93; 95% CI 0.84 to 1.03), while dapagliflozin was superior to placebo in reducing the composite of cardiovascular death or hospitalization for heart failure (HR 0.83; 95% CI 0.73 to 0.95). The latter finding, however, was due to the lower rate of hospitalization for heart failure in the dapagliflozin group (HR 0.73; 95% CI 0.61 to 0.88) and not due to an effect on cardiovascular mortality. Dapagliflozin significantly reduced by 24% the incidence of the composite kidney outcome of more than 40% reduction in eGFR, new end-stage renal disease, or death from renal or cardiovascular causes [51].

The Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV) examined the cardiovascular effects of ertugliflozin (5 mg or 15 mg) compared to placebo in 8246 people with type 2 diabetes and established atherosclerotic cardiovascular disease involving the coronary, cerebrovascular, or peripheral artery systems [50]. During a median follow-up of 3.0 years, ertugliflozin was non-inferior, but not superior, to placebo in terms of MACE (HR 0.97; 95% CI 0.85 to 1.11), its individual components, and the composite kidney outcome of death from renal causes, renal replacement therapy, or doubling of serum creatinine. Consistent with other SGLT-2 inhibitors, ertugliflozin reduced the incidence of hospitalization for heart failure versus placebo with an HR of 0.70 (95% CI 0.54 to 0.90) [50].

Based on the results of individual cardiovascular outcomes trials, all four SGLT-2 inhibitors consistently reduced hospitalization for heart failure, all SGLT-2 inhibitors except ertugliflozin improved kidney outcomes, while empagliflozin and canagliflozin had a beneficial effect on MACE. These findings were synthesized in a meta-analysis that produced pooled estimates for all SGLT-2 inhibitors as a drug class and explored the heterogeneity of outcomes assessed by individual SGLT-2 inhibitors in the overall class [92]. Results of this meta-analysis showed that the predominant beneficial effect of SGLT-2 inhibitors was the reduction in hospitalization for heart failure compared to placebo, with an HR of 0.68 (95% CI 0.61 to 0.76). This estimate was highly consistent with no evidence of statistical heterogeneity across the class, given that a significant effect in favour of the SGLT-2 inhibitor arm was achieved in each individual trial. An overall beneficial effect of SGLT-2 inhibitors

was also shown on MACE (HR 0.90; 95% CI 0.85 to 0.95) and on cardiovascular mortality (HR 0.85; 95% CI 0.78 to 0.93); however, a significant degree of heterogeneity was observed in the analyses for both outcomes, especially cardiovascular mortality, reflecting possible differences between individual SGLT-2 inhibitors in terms of their effects on atherosclerotic events [92]. Some degree of heterogeneity was also present in the analysis for the composite kidney endpoint (HR 0.62; 95% CI 0.56 to 0.70), most likely due to VERTIS-CV trial, as ertugliflozin was the only SGLT-2 inhibitor without a demonstrated benefit on kidney outcomes. Another potential source of heterogeneity could be the fact that there were differences in the components of the composite kidney outcome across trials [92]. In this regard, a meta-analysis focusing on the renal effects of SGLT-2 inhibitors used more consistent definitions across trials with canagliflozin, dapagliflozin, and empagliflozin for clinically important kidney outcomes [93]; based on this meta-analysis, the three SGLT-2 inhibitors improved all kidney outcomes with no evidence of heterogeneity between trials [93].

As for GLP-1RAs, it is clinically relevant to establish whether the observed effects of SGLT-2 inhibitors in people with type 2 diabetes and increased cardiovascular risk are consistent regardless of history of established atherosclerotic disease. Meta-analyses of cardiovascular outcomes trials that assessed the effects of SGLT-2 inhibitors in two subgroups according to the presence of established atherosclerotic cardiovascular disease did not find evidence of a modification effect regarding the overall beneficial effect of SGLT-2 inhibitors versus placebo on MACE, cardiovascular mortality, hospitalization for heart failure, and a composite kidney outcome [92]. However, data for the subgroup of participants without atherosclerotic disease (individuals with multiple risk factors only) were available only for dapagliflozin and canagliflozin [92].

Although long-term head-to-head trials comparing GLP-1RAs with SGLT-2 inhibitors are lacking, indirect comparisons from network meta-analyses found that both classes confer comparable benefits on all-cause mortality, cardiovascular mortality, and MACE [26,94,95]. Moreover, GLP-1RAs might be more effective in preventing stroke, whereas SGLT-2 inhibitors reduce hospitalizations for heart failure [26,94,95]. Some intraclass differences between agents might also exist, but it is unclear whether these comparative estimates are clinically meaningful [26]. A complementary source of comparative effectiveness evidence is large registry-based cohort studies utilizing real-world data of new users of GLP-1RAs or SGLT-2 inhibitors. In particular, five cohort studies have corroborated the superiority of SGLT-2 inhibitors over GLP-1RAs in reducing heart failure hospitalizations [96–100], whereas two of these studies also found that SGLT-2 inhibitors were more effective in reducing a composite cardiovascular endpoint [96,97]. Interestingly, emerging data suggest that, due to their different mechanisms of action, both drug classes may be considered as combination therapy to enhance their favourable effect on metabolic variables and possibly to provide complementary cardiovascular benefits [1,101,102].

Evidence from kidney outcomes trials

Secondary and exploratory analyses of type 2 diabetes cardiovascular outcomes trials suggested that SGLT-2 inhibitors can improve kidney outcomes; however, none of these trials was designed to assess kidney outcomes specifically in people with chronic kidney disease [49–52]. In this regard, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial was the first large-scale randomized trial to assess the effects of canagliflozin on kidney outcomes in people with type 2 diabetes and albuminuric chronic kidney disease, the latter defined as an eGFR of 30 to <90 ml/min/1.73 m^2 and a urinary albumin-to-creatinine ratio of >300 [57]. The 4401 participants were randomized to either canagliflozin 100 mg or placebo, and were followed over a median period of 2.6 years. Stable treatment (for at least four weeks before randomization) with an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker was a prerequisite for all eligible participants. The primary composite outcome of end-stage kidney disease, or doubling of serum creatinine level, or death from renal or cardiovascular causes occurred in significantly fewer participants receiving canagliflozin with an HR of 0.70 (95% CI 0.59 to 0.82). Additionally, treatment with canagliflozin reduced the risk for MACE by 20% and for the composite of cardiovascular death or hospitalization for heart failure by 31% [57].

The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial was based on the same rationale, aiming to assess the kidney and cardiovascular effects of dapagliflozin in a dedicated chronic kidney disease population [58]. However, in contrast to CREDENCE, the primary hypothesis in DAPA-CKD was that the kidney effects of dapagliflozin occur in people with chronic kidney disease irrespective of the presence of type 2 diabetes. As such, DAPA-CKD included a considerable number of participants without type 2 diabetes at baseline (~32.5% of the 4304 participants). Moreover, in its eligibility criteria, DAPA-CKD used lower thresholds than CREDENCE both for eGFR (25–75 ml/min/1.73 m^2) and for albuminuria (urinary albumin-to-creatinine ratio of >200) [58]. The primary composite kidney outcome was reduced by 39% (HR 0.61; 95% CI 0.51 to 0.72) in the dapagliflozin arm. Treatment with dapagliflozin was also associated with a lower incidence of all-cause mortality (HR 0.69; 95% CI 0.53 to 0.88) and of the composite of cardiovascular mortality or hospitalization for heart failure (HR 0.71; 95% CI 0.55 to 0.92) [58]. Subgroup analyses of DAPA-CKD indicated that these effects were consistent regardless of presence of type 2 diabetes [103].

Both CREDENCE and DAPA-CKD required the presence of macroalbuminuria for inclusion in addition to reduced eGFR. In contrast, the Effect of sotagliflozin on cardiovascular and renal events in patients with type 2 diabetes and moderate renal impairment who are at cardiovascular risk (SCORED) trial evaluated the dual SGLT-2 and SGLT-1 inhibitor sotagliflozin in people with type 2 diabetes and chronic kidney disease, regardless of the degree of albuminuria [104]. The original two primary outcomes in SCORED were MACE and the composite of cardiovascular mortality or hospitalization for heart failure; however, due to the trial's early cessation and the subsequent fewer than planned accrued number of events, the primary outcome was changed to the total number of cardiovascular deaths, hospitalizations for heart failure, and urgent visits for heart failure. During a median follow-up of 16 months, the primary outcome occurred in fewer people in the sotagliflozin arm, compared with placebo (HR 0.74; 95% CI 0.63 to 0.88) [104]. Sotagliflozin has not received marketing approval for type 2 diabetes.

Empagliflozin in patients with chronic kidney disease (EMPA-KIDNEY) is an event-driven randomized trial evaluating the effect of empagliflozin 10 mg against placebo on the primary outcome of kidney disease progression or cardiovascular death in people with chronic kidney disease [105]. Between May 2019 and April 2021,

6609 participants were randomized, of whom 44% had type 2 diabetes and 27% had a history of cardiovascular disease. Trial results are anticipated in the near future [105].

A meta-analysis has synthesized cardiovascular outcomes trials and kidney outcomes trials of SGLT-2 inhibitors, using data only for people who had both type 2 diabetes and chronic kidney disease across all trials [106]. In this population, SGLT-2 inhibitors, compared to placebo, reduced MACE by 17%, hospitalization for heart failure by 38%, and a kidney composite outcome by 34%. Individual MACE components and all-cause mortality were also significantly reduced with SGLT-2 inhibitors. In addition, beneficial effects of SGLT-2 inhibitors on MACE, hospitalization for heart failure, and kidney outcomes were evident even in the subgroup of participants with an eGFR of <45 ml/min/1.73 m^2 [106].

With regard to GLP-1RAs, no dedicated kidney outcomes trial is currently available. However, cardiovascular outcomes trials with GLP-1RAs have included people with an eGFR as low as 15 ml/min/1.73 m^2 [85]. A meta-analysis of eight cardiovascular outcomes trials found that the overall beneficial effect of GLP-1RAs on MACE (HR 0.85; 95% CI 0.78 to 0.93) was consistent between those with an eGFR of ≤60 ml/min/1.73 m^2 and the subgroup with an eGFR of >60 ml/min/1.73 m^2, as suggested by the non-significant value of the statistical test for subgroup differences [85]. More definitive evidence about the kidney and cardiovascular effects of GLP-1RAs in people with chronic kidney disease are expected on completion of the FLOW trial (NCT03819153), which is evaluating whether subcutaneous semaglutide can slow the progression of chronic kidney disease in people with type 2 diabetes and renal impairment [107].

Evidence from heart failure trials

People with type 2 diabetes have an increased risk of developing heart failure, which further increases morbidity, mortality, and occurrence of other adverse outcomes (Chapter 50). Therefore, careful consideration should be paid when choosing among pharmacological treatment options in those individuals with type 2 diabetes with established or high risk for developing heart failure. Pioglitazone should be avoided because it has been associated with an increased risk of heart failure [108]. Cardiovascular outcomes trials suggest that DPP-4 inhibitors have a neutral effect on heart failure outcomes, except for saxagliptin, which was associated with a higher rate of hospitalization for heart failure versus placebo (3.5% vs 2.8%) in the Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus–Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53) trial [36]. Caution is therefore warranted if saxagliptin is used in people with a history of heart failure. Meta-analyses of cardiovascular outcomes trials have found a modest effect of GLP-1RAs in reducing hospitalization for heart failure that was marginally significant [85,89]. Although it is unclear whether this finding is clinically meaningful, it deserves to be further examined. The effect of the GIP/GLP-1 receptor agonist tirzepatide on heart failure endpoints in people with heart failure with preserved ejection fraction and obesity is being evaluated in the Study of tirzepatide in participants with heart failure with preserved ejection fraction and obesity (SUMMIT) trial (NCT04847557). A considerable beneficial effect on heart failure outcomes, in particular hospitalization for heart failure, has been shown consistently in all cardiovascular outcomes trials with SGLT-2 inhibitors. As a result, agents from this drug class have subsequently been evaluated in large-scale trials that focused on people with heart failure and assessed heart failure outcomes as their primary endpoint.

The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial was the first dedicated heart failure trial with an SGLT-2 inhibitor. DAPA-HF randomized a total of 4744 participants with New York Heart Association (NYHA) class II, III, or IV heart failure and reduced ejection fraction (≤40%) to either dapagliflozin or placebo [55]. Over a median duration of 18.2 months, the primary composite outcome of worsening of heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death occurred in fewer participants receiving dapagliflozin (HR 0.74; 95% CI 0.65 to 0.85). This beneficial effect was also evident in the subgroup of participants who had type 2 diabetes (42% of the trial population). Treatment with dapagliflozin significantly improved the individual components of the primary outcome and all-cause mortality [55]. The Empagliflozin outcome trial in people with chronic heart failure and a reduced ejection fraction (EMPEROR-Reduced) used the same key eligibility criteria (heart failure with reduced ejection fraction) and the same primary outcome as DAPA-HF [54]. During a median follow-up of 16 months, empagliflozin 10 mg reduced the risk of the primary outcome by 25% versus placebo, an effect that was consistent in the subgroup of participants with diabetes (~50% of the 3730 participants) [54]. A meta-analysis pooling data from both trials concluded that dapagliflozin and empagliflozin consistently reduced the composite of hospitalization for heart failure and cardiovascular death by ~25% in people with heart failure and reduced ejection fraction, regardless of the presence or absence of type 2 diabetes [109].

In the Empagliflozin outcome trial in patients with chronic heart failure and a preserved ejection fraction (EMPEROR-Preserved), empagliflozin was assessed in individuals with heart failure with preserved ejection fraction (>40%) [53]. The 5988 participants, 49% of whom had diabetes, were randomized to either empagliflozin 10 mg or placebo and were followed over a median of 26.2 months. The primary composite outcome of cardiovascular death or hospitalization for heart failure occurred in fewer participants assigned to empagliflozin compared with placebo (HR 0.79; 95% CI 0.69 to 0.90), an effect that was mainly related to a lower risk of hospitalization for heart failure (HR 0.73; 95% CI 0.61 to 0.88). In a subgroup analysis, these findings appeared consistent regardless of the presence of diabetes [53]. Individuals with heart failure with preserved ejection fraction are also the focus of the Dapagliflozin Evaluation to improve the LIVEs of patients with pReserved ejection fraction heart failure (DELIVER) trial, a randomized trial examining whether dapagliflozin is superior to placebo in reducing the composite of worsening heart failure or cardiovascular death [110]. Recruitment in DELIVER was completed in January 2021 with 6263 participants and an anticipated median follow-up of 27 months [110].

The Effect of sotagliflozin on cardiovascular events in patients with type 2 diabetes post worsening heart failure (SOLOIST-WHF) trial compared the dual SGLT-2 and SGLT-1 inhibitor sotagliflozin with placebo over a median of 9.0 months in 1222 people with heart failure with either reduced or preserved ejection fraction [111]. All participants had type 2 diabetes and were recently hospitalized for worsening heart failure. The rate of the primary outcome of the total number of cardiovascular deaths, hospitalizations, and urgent visits for heart failure (first and subsequent events) was significantly lower in the sotagliflozin group than in the placebo group (HR 0.67; 95% CI 0.52 to 0.85) and this benefit was consistent in the two prespecified subgroups of participants with an ejection fraction <50% and ≥50%. SOLOIST-WHF was originally designed to assess

the primary outcome of cardiovascular death or hospitalization for heart failure in ~4000 participants; however, its primary endpoint was changed because, similar to the SCORED trial, the trial ended early due to lack of funding [111].

Apart from these heart failure trials, additional evidence supporting the beneficial effects of SGLT-2 inhibitors in people with heart failure comes from subgroup analyses of the original cardiovascular outcomes trials that recruited people with type 2 diabetes and increased cardiovascular risk. In particular, a meta-analysis synthesized data from EMPAREG-OUTCOME, CANVAS Program, DECLARE-TIMI 58, and VERTIS CV and compared the cardiovascular effects of SGLT-2 inhibitors between the two subgroups of people with and without heart failure within the overall populations of all four trials [92]. The findings showed that SGLT-2 inhibitors reduce the composite of cardiovascular death or hospitalization for heart failure in both subgroups [92]. Based on the overall evidence both from cardiovascular outcomes trials and from heart failure trials, the SGLT-2 inhibitor class consistently confers clinically important benefits in heart failure endpoints in people who have either type 2 diabetes, or heart failure, or both.

Management of obesity and associated comorbidities

The obesity epidemic is paralleled not only by the increasing prevalence of type 2 diabetes, but also by other cardiometabolic adverse effects, including high blood pressure, elevated cholesterol and triglyceride levels, liver steatosis and fibrosis, obstructive sleep apnoea, and most importantly cardiovascular disease. Promoting weight loss through increased physical activity and energy restriction plays a key role in the management of type 2 diabetes, but behavioural changes are hard to implement. Sulfonylureas, pioglitazone, as well as basal insulin are associated with weight gain, while metformin and DPP-4 inhibitors have a neutral effect on body weight. By contrast, GLP-1RAs induce weight loss by slowing gastric emptying and by promoting satiety, while treatment with SGLT-2 inhibitors leads to urinary excretion of excess calories due to glucosuria. Use of agents from these two classes, in particular GLP-1RAs, results in sustainable weight reduction and, as such, people with type 2 diabetes for whom weight loss or maintenance is a therapeutic priority should be treated preferably with a GLP-1RA or an SGLT-2 inhibitor [1, 6]. Certain GLP-1RAs including liraglutide and subcutaneous semaglutide have received marketing authorization at higher doses for chronic weight management irrespective of the presence of type 2 diabetes. Based on a network meta-analysis assessing pharmacological therapies for obesity, high-dose semaglutide is likely the most effective agent, achieving body weight reductions that could be as high as 10% [112]. In addition, currently available data from randomized controlled trials suggest that in people with type 2 diabetes the dual GIP/GLP-1 receptor agonist tirzepatide has an impressive weight-lowering potential, superior to that of subcutaneous semaglutide [61]. The effect of tirzepatide as an anti-obesity medication is being investigated in the ongoing Study of tirzepatide in participants with obesity or overweight (SURMOUNT) clinical trial programme.

People with type 2 diabetes who have overweight or obesity often have comorbid NASH, which currently represents the most common liver disorder in Western countries and has become the leading indication for liver transplantation in the USA. Insulin resistance is a shared characteristic of type 2 diabetes and obesity and is considered as a key pathogenic driver of NASH. Despite the growing prevalence of the condition, management is largely based on lifestyle modification and treatment of individual components of the metabolic syndrome, due to lack of licensed disease-specific interventions that could prevent progression of hepatic steatosis to liver fibrosis and cirrhosis [113]. Nevertheless, emerging evidence suggests that certain anti-diabetes drugs including pioglitazone, GLP-1RAs, and to a lesser extent SGLT-2 inhibitors might have a favourable effect on NASH. Based on liver biopsy studies, pioglitazone was associated with reductions in hepatic steatosis and lobular inflammation, but not with improvement in fibrosis score [114]. Treatment with liraglutide and semaglutide resulted in histological resolution of NASH and halted progression of fibrosis [115, 116]. Studies utilizing mostly magnetic resonance–based techniques for assessment of liver fat content have also suggested potential benefits for dulaglutide as well as several SGLT-2 inhibitors, including canagliflozin, dapagliflozin, empagliflozin, and ipragliflozin [117, 118]. On the basis of this evidence, the American Association of Clinical Endocrinology advocates the use of pioglitazone or GLP-1RAs for people with type 2 diabetes and biopsy-proven NASH [113]. Both drug classes should be considered when there is an elevated probability of having NASH based on elevated plasma aminotransferase levels and non-invasive tests, while GLP-1RAs, pioglitazone, or SGLT2 inhibitors can probably be considered to offer cardiometabolic benefit in people with type 2 diabetes and non-alcoholic fatty liver disease (NAFLD) [113].

For people with type 2 diabetes and morbid obesity, bariatric surgery is a highly effective alternative for weight loss compared with lifestyle and medical interventions that confers superior glycaemic and other metabolic management, mitigates cardiovascular risk, and may even provide survival benefits. Metabolic surgery often reduces the number of anti-diabetes medications needed to restore euglycaemia and can induce remission of diabetes and clearance of NASH. The procedure is generally safe when performed in high-volume centres with experience in gastrointestinal surgery. Bariatric surgery is therefore recommended to treat type 2 diabetes in screened surgical candidates with BMI $\geq$40 kg/m^2, as well as in people with BMI 35–40 kg/m^2 who do not achieve durable weight loss and improvement in comorbidities (including hyperglycaemia) with non-surgical methods. Bariatric surgery could also be considered in people with type 2 diabetes with BMI 30–34 kg/m^2 [119].

Precision medicine–based approach

An alternative approach for choosing among anti-diabetes medications is in line with the concept of precision medicine and suggests that people with type 2 diabetes can be clustered into five distinct subgroups according to various clinical variables, such as age at onset of diabetes, HbA_{1c}, BMI, or measures of insulin resistance [120]. These subgroups have been reproduced in large-scale populations and have been associated with different risks of developing diabetes-related complications and responses to specific treatments. Based on this rationale, certain drugs can be more efficacious for specific clinical phenotypes of type 2 diabetes. In particular, it has been suggested that insulin and insulin secretagogues are likely the therapy of choice for the clusters of severe autoimmune diabetes (SAID) and severe insulin-deficient diabetes (SIDD), insulin sensitizers for people with severe insulin-resistant diabetes (SIRD), and metformin for mild obesity-related diabetes (MOD) [120]. A recent study aiming to validate these novel subtypes in the DEVOTE, LEADER, and SUSTAIN-6 cardiovascular outcomes trials found that the highest risk for cardiovascular events

was evident in participants with high HbA_{1c} and low BMI who most closely resembled the SIDD cluster [121]. Nevertheless, this suggested classification system of diabetes should not be considered final at present, as it is still evolving and requires further refinements to achieve better predictive power [120].

Therapeutic decision making in the clinical setting

Currently, choice of appropriate anti-diabetes therapy is primarily guided by the presence of clinically important comorbidities and underlying cardiovascular risk. For people with type 2 diabetes and chronic kidney disease, SGLT-2 inhibitors are most likely better suited due to their kidney and cardiovascular protection, whereas a long-acting GLP-1RA is recommended for individuals who cannot use an SGLT-2 inhibitor [122]. SGLT-2 inhibitors should also be prioritized in people with type 2 diabetes and heart failure [1, 80, 123]. Specific GLP-1RAs and SGLT-2 inhibitors are recommended for people with type 2 diabetes and with established atherosclerotic disease or with multiple cardiovascular risk factors [1, 2, 80]. The level of certainty in this recommendation is probably higher for the former subgroup, because some cardiovascular outcomes trials have focused exclusively on people with established cardiovascular disease, while in trials that recruited both subgroup populations fewer events were recorded for participants with multiple risk factors only. Although the definition used for multiple risk factors was not identical among these trials, in most cases it comprised a combination of at least three risk factors such as dyslipidaemia, obesity, smoking, age, or hypertension. The cardiovascular benefits of GLP-1RAs and SGLT-2 inhibitors appear to be independent of their glucose-lowering effect and of prior metformin use [124–126]; it is therefore reasonable to treat people who have type 2 diabetes and any of the cardiovascular comorbidities mentioned with these agents irrespective of baseline HbA_{1c} or metformin therapy [2].

It is unclear, however, whether the favourable cardiovascular effects of GLP-1RAs or SGLT-2 inhibitors are applicable to people with type 2 diabetes who have fewer than three risk factors. In this regard, a network meta-analysis of 298 randomized controlled trials found no clinically meaningful differences between anti-diabetes medications for mortality and vascular outcomes in people at low cardiovascular risk [26]. Another network meta-analysis estimated absolute effects of treatment with GLP-1RAs and SGLT-2 inhibitors on cardiovascular and kidney outcomes for different categories of baseline cardiovascular risk. In particular, relative effect estimates from pooled trial data, which were largely driven by cardiovascular outcomes trials, were combined with baseline risk estimates derived from epidemiological data [95]. The estimated absolute treatment effects were very low for people with few or no cardiovascular risk factors, leading to a weak recommendation regarding the use of either a GLP-1RA or an SGLT-2 inhibitor in this population [95, 127]. This underlines not only the importance of prudent use of finite resources, but also the need to consider and avoid increased treatment burden and potential side effects that might be associated with the use of agents for cardiorenal protection in people with very low absolute cardiovascular risk. As such, key drivers for therapeutic decisions in people with low underlying risk are management of glycaemia, body weight, or associated morbidities such as NASH. Metformin remains the agent of choice for treatment of hyperglycaemia in most cases, including newly diagnosed type 2 diabetes, due to the extensive experience with its use, overall efficacy and safety profile, and affordability [1, 80]. In the presence of obesity or NASH, specific medications are preferable, such as GLP-1RAs or SGLT-2 inhibitors for the former, and pioglitazone and some GLP-1RAs for the latter condition.

Additional important considerations can affect real-life therapeutic decisions and people's willingness to follow these decisions. For example, treatments with increased hypoglycaemic risk, such as sulfonylureas or intensive insulin regimens, should be avoided in individuals in whom hypoglycaemia can be life threatening. Moreover, agent- or class-specific adverse events, such as gastrointestinal adverse events with metformin or with GLP-1RAs, can limit the use of these medications in some people. Pharmacological treatment of older people with diabetes and frailty should also be given special attention; in particular, despite the cardiovascular benefits of GLP-1RAs or SGLT-2 inhibitors even in older populations [128], treatment with these agents is often not feasible due to practical concerns (e.g. need for subcutaneous administration of GLP-1RAs), susceptibility to dangerous side effects (e.g. falls due to volume depletion caused by SGLT-2 inhibitors), or drug availability and affordability issues. With respect to the latter, diabetes and the associated costs of managing the disease and its complications affect ethnic minorities and low-income populations disproportionally. Beyond novel therapies, increased emphasis on social determinants of health is even more necessary to tackle disparities and ensure humane and affordable care for all people with type 2 diabetes [129].

It is equally important that clinical decisions attend to the values and preferences of the informed individual with type 2 diabetes. This person-centred approach means that it is not the clinician who should exclusively make therapeutic decisions: it is an ethical imperative that the affected individual participates as an equal partner in decision making. Personal values and preferences may include experience of former and current related illnesses, other relevant life experiences, health habits, goals and expectations, social or family support, or personal beliefs about medical interventions. Depending on these factors, people may have polarized perceptions, ranging from no specific views to concrete predispositions, on how to proceed with their treatment. Research has suggested that considerable variation can also exist between the preferences of physicians and those of people with type 2 diabetes when it comes to weighting the merits and drawbacks of available medications [130]. Moreover, people's actions may also deviate from the preferences and views they themselves had previously expressed during the clinical consultation with their physician.

Keeping these in mind and given the complex and chronic nature of type 2 diabetes, as well as the constantly evolving diabetes research informing guidelines formulation, clinicians should not only continually update their knowledge on the pharmacological management of the disease, but also regularly reassess the overall health profile, relevant comorbidities, and personal perceptions of those they treat. By doing so, meaningful deliberations between caregivers and individuals affected by type 2 diabetes can be achieved, leading to well-informed decisions with minimal treatment burden that motivate both parties to mutually collaborate in a holistic management plan.

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38 Weight Management and Metabolic Surgery

Alexis Sudlow[1], Dimitri J. Pournaras[1], and Carel W. le Roux[2]

[1] Department of Bariatric Surgery, Southmead Hospital, Bristol, UK

[2] Diabetes Complications Research Centre, University College Dublin, Dublin, Ireland

Key points

- Weight loss in its own right is increasingly being recognized as an important therapeutic target for people with obesity and type 2 diabetes, which can be achieved using several different modalities. The key to the success of any treatment is weight loss that is maintained.
- Lifestyle modification including caloric restriction can produce clinically significant weight loss; however, sustaining this long term is challenging. Evidence to demonstrate a resultant improvement in cardiovascular risk factors or mortality is limited.
- Evidence from more than 13 randomized controlled trials has consistently demonstrated that, irrespective of the procedure performed, bariatric surgery is more effective than medical therapy for the treatment of obesity and type 2 diabetes.
- The recent development of a number of medications producing clinically significant weight loss may present new treatment options to a wider demographic of people than surgery.

Weight loss in itself and weight management in people with type 2 diabetes allow for the alteration of the primary disease process, obesity. In those with impaired glucose tolerance or early diabetes it may prevent disease progression or induce remission, whereas for those with established disease it may improve glycaemic levels while reducing treatment burden. Additionally, for those with complications of type 2 diabetes, such as macrovascular complications, sustained weight loss may actually prevent progression or reversal of established complications, including diabetic kidney disease [1]. Like any intervention, the individual benefit of weight loss to those with type 2 diabetes will vary and may be of most value in those primarily with insulin resistance, while those with β-cell dysfunction will likely benefit to a lesser degree.

In addition to improving glycaemic levels, the treatment of hypertension and dyslipidaemia, in their own right, is critical in reducing the risk of cardiovascular death. It is also recognized that weight-based therapeutic goals have a place in the management of individuals with obesity and type 2 diabetes. Weight reduction not only presents the opportunity to modify the underlying disease process, but has further metabolic benefits, including a reduction in the systemic inflammatory response, and improved blood pressure, dyslipidaemia, and quality of life. Although there are many therapeutic interventions available to aid weight loss, it is important to recognize that sustained long-term weight loss is critical to improving clinically relevant outcomes. The heterogeneous nature of both type 2 diabetes and obesity means there will be a degree of inter-individual variation in response to any single treatment. The availability of different treatment modalities presents the opportunity to implement an individualized approach to weight management as well as the potential to combine treatments, which may act by complementary but distinct mechanisms.

Diet, lifestyle, and psychological support

Owing in part to the perceived simplicity and relatively low cost, diet and lifestyle interventions have long been favoured as a means of promoting weight loss in individuals with obesity and type 2 diabetes, with the aim of reducing glycaemic levels, inflammatory markers, as well as cardiovascular risk factors. Although several studies have demonstrated that weight loss through diet or exercise-based interventions resulted in improved glycaemic levels and cardiovascular risk factors, including lipids and blood pressure, questions remained regarding the impact of these interventions on the risk of cardiovascular morbidity and mortality [2–4]. The Look AHEAD (Action for Health in Diabetes) trial demonstrated that an intensive lifestyle modification programme achieved clinically significant weight loss with a concomitant improvement in glycated haemoglobin (HbA_{1c}) and cardiovascular risk factors aside from low-density lipoproteins (LDL). In spite of this, the trial was stopped early on the basis of futility, as it did not result in a reduction in the primary endpoint of decreased rates of cardiovascular events [5]. A *post hoc* analysis of the results, however, showed a relationship between the magnitude of weight loss and improved cardiovascular risk. In individuals who lost >10% of their body weight in the first year, there was a 21% reduction in the risk of fatal and non-fatal cardiovascular events [6].

More recently, the implementation of a very low-calorie diet (VLCD) or total meal replacement has garnered increasing attention, in part due to the results of the Diabetes Remission Clinical Trial (DiRECT). The primary care–led intervention comprised a strict 12–20-week period of 800 kcal/d weight loss phase, during which the individuals had only formula diet, followed by food

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reintroduction and structured support for weight loss maintenance. Of the individuals in the intervention arm, 46% and 36% were in remission from type 2 diabetes after one and two years, respectively, with sustained weight loss being linked to the maintenance of remission [7]. Although this study demonstrated promising results with regard to diabetes remission following significant weight loss, it also highlighted the critical issue surrounding dietary or lifestyle interventions as a means of treating type 2 diabetes, namely the sustainability of the intervention and resultant ability to maintain weight loss. At one year, nearly 25% of the participants demonstrated a 15 kg weight loss, which fell to just 11% after two years, which in part likely represents a proportion of individuals who were no longer able to follow the diet as prescribed.

With all dietary or lifestyle interventions, the aim of inducing weight loss through a caloric deficit remains valid and in most cases is effective in the short term in producing volitional weight loss. However, they are unsustainable for many individuals in the long term, with subsequent weight regain. Critically, VLCD and total meal replacement, in particular, do not address the underlying disease process of obesity and may only exacerbate hunger, which reduces the likelihood of long-term weight loss maintenance. In spite of this, dietary interventions may be effective in a small subgroup of individuals and may have a role for those who have not previously been on supervised weight loss programmes, as they are a low-risk intervention. Clinicians should be mindful that the majority of individuals will require treatment intensification with the addition of alternative modalities to produce clinically relevant and sustained weight loss.

Prior to undergoing bariatric surgery, people with obesity are typically advised to engage in a supervised weight loss programme; however, the duration and exact structure are variable. Preoperative weight loss is positively correlated in some studies with increased postoperative weight loss, fewer complications, as well as a reduction in liver volume, which facilitates surgical access [8,9]. Dietary changes are required in the postoperative period and generally involve modifying eating patterns to include regular, small meals, high in protein, while following supplementation guidelines, which vary according to the type of surgery. In the postoperative period there is no evidence to support that participation in a supervised exercise programme alone results in significant additional weight loss or preservation of lean mass [10,11]. In spite of this, studies have demonstrated that engagement with a regular exercise programme following bariatric surgery can increase cardiorespiratory fitness, strength, and physical function and people undergoing surgery are generally advised to engage in regular physical activity [11–13].

Psychological support is a central element in the multidisciplinary management of people with obesity, particularly those undergoing bariatric surgery in both the preoperative and postoperative periods. As such, bariatric surgery should only be provided in units where psychological support is available [14]. People with obesity are more likely to suffer from psychological issues including anxiety, depression, poor self-image, prior trauma, and disordered eating, which all have implications for quality of life [15,16]. The identification of maladaptive eating behaviours preoperatively, including binge eating and emotional eating, is important as they are unlikely to be improved following surgery and are associated with poorer weight loss outcomes [17].

The British Obesity Metabolic Surgery Society guidelines have broken the psychological support pathway into a pre- and postoperative stepped model involving three levels: online support, group workshops, and individualized support delivered by a trained psychologist [18]. During the preoperative period, the role of psychological support is not to screen out those who are unsuitable for surgery, but rather to identify potential barriers to weight loss or success with bariatric surgery and implement support where possible. Psychological support is critical to helping those undergoing surgery to identify the means of setting realistic expectations, as well as strategies for how they will adapt and manage the challenges in the postoperative period [18]. Some people with previously well-managed mental health issues may experience a period of destabilization, including those with substance misuse disorders.

Pharmacotherapy

The ideal anti-obesity pharmacotherapy is theoretically one that is more effective than dietary or lifestyle intervention, while being less invasive and potentially available to a wider demographic than bariatric surgery. Until recently no such agent existed, with many of the previously available drugs being either ineffective, dangerous, or both. Widespread media coverage of serious side effects linked to the use of now recalled medications such as sibutramine and phentermine/fenfluramine has contributed to a general reluctance from both clinicians and individuals with obesity to consider their use. In recent years, there has been remarkable progress made in the development of novel agents, which show excellent tolerability and safety while promoting clinically significant weight loss. These may further broaden the availability of therapeutic options for those with obesity and type 2 diabetes. Broadly speaking, these novel agents can be divided into two main subclasses: anti-obesity medications that are specifically targeting weight loss; and diabetes medications that are primarily licensed for treating hyperglycaemia but also promote weight loss.

Anti-obesity medications

Orlistat is a gastric and pancreatic lipase inhibitor, which works primarily by reducing the absorption of dietary fat. Randomized controlled trials (RCTs) have shown that orlistat can result in a 5–10% weight loss associated with an improvement in glycaemic levels and cardiovascular risk factors [19,20]. It is associated with gastrointestinal symptoms, particularly diarrhoea, and is often poorly tolerated, largely limiting its long-term use.

More recently developed anti-obesity medications largely act centrally to produce appetite suppression, which may in part be responsible for the decreased incidence of gastrointestinal side effects and greater tolerability. The combination of naltrexone and bupropion acts in a synergistic manner, with bupropion activating proopiomelanocortin (POMC) receptor neurons in the arcuate nucleus to decrease appetite and naltrexone further enhancing this effect. The COR-II trial demonstrated its efficacy in promoting weight loss in individuals with obesity, with nearly one-third of participants achieving >10% weight loss after 56 weeks of treatment [21].

Another combined anti-obesity medication, phentermine and topiramate, produces appetite suppression and also alters energy balance, resulting in weight loss and concomitant improvements in glycaemic levels. The CONQUER study demonstrated that in those with type 2 diabetes, there was a mean weight loss of 9.4% after a 56-week period of treatment associated with 37% of the individuals achieving an HbA_{1c} <6.5% (48 mmol/mol) despite a reduced need for diabetes medications [22].

Coming from the same drug class as fenfluramine, which has been withdrawn, lorcaserin is a selective 5-HT_{2c} agonist that produces appetite suppression through activation of POMC neurons. In the Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus (BLOOM-DM) 52-week placebo-controlled trial, lorcaserin produced a >5% weight reduction from baseline in 44.7% of people with type 2 diabetes [23]. A reduction in HbA_{1c} was also seen, with 52% of participants achieving a level of <7% (53 mmol/mol) at one year. Lorcaserin use is not associated with the valvular defects seen with fenfluramine, which were thought to be secondary to increased mitotic activity mediated via its effect on 5-HT_{2B} receptors [24]. The market approval for lorcaserin, however, was withdrawn because of an increased occurrence of cancer during a safety clinical trial.

Although none of these drugs in themselves directly mediates changes in glycaemic levels, the weight loss they produce may modify the underlying disease process of type 2 diabetes and improve glucose metabolism.

Anti-diabetes medications

Several medications that were initially licensed to treat type 2 diabetes induce significant weight loss and there is increasing interest in how indications for their use can be expanded (Table 38.1). Mimicking some of the neurohormonal changes induced by bariatric surgery, glucagon-like peptide-1 (GLP-1) receptor agonists, including semaglutide, liraglutide, and dulaglutide, produce not only improved glycaemic levels, but clinically significant reductions in body weight and cardiovascular risk factors, including blood pressure and lipids. These medications act in a glucose-dependent manner to stimulate insulin secretion while inhibiting glucagon production and therefore have a low risk of hypoglycaemia [25]. They also act to modulate hunger within the gastrointestinal tract by slowing gastric emptying as well as centrally, promoting satiety by activating receptors in the arcuate nucleus of the hypothalamus. Clinical trials involving both liraglutide and semaglutide have demonstrated that 33% and 13% of the individuals achieve 10% weight loss, respectively [26, 27]. Critically, in people with type 2 diabetes, the use of GLP-1 receptor agonists reduces the risk of fatal and non-fatal cardiovascular events.

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors act by decreasing the renal reabsorption of glucose, which not only improves glycaemia but results in clinically significant weight loss through an obligate calorie loss in the urine. A pooled analysis of outcomes of phase three trials comparing canagliflozin to placebo demonstrated that 25% of the individuals had >5% weight loss [28]. There were also weight-dependent improvements in HbA_{1c} and systolic blood pressure, with weight loss accounting for 15% and 42% of changes in each, respectively. The use of both canagliflozin, dapagliflozin, and empagliflozin reduces fatal and non-fatal cardiac events, with the EMPA-REG OUTCOME trial demonstrating a 38% relative risk reduction in fatal cardiovascular events with empagliflozin compared to placebo in people with type 2 diabetes [29, 30].

When considering the use of weight loss pharmacotherapy, there remain questions regarding timing and indications for initiation and stopping. Anti-obesity medications remain an underutilized treatment modality for individuals with obesity and type 2 diabetes, in part because of perceptions regarding efficacy and safety. These concerns are not reflective of the currently available medications and diabetes drugs that promote weight loss are increasingly being used.

Anti-obesity medications may be useful in the pre- and postoperative periods for individuals undergoing bariatric surgery [31]. It is well recognized that a proportion of people will experience weight gain or a plateau of weight loss following bariatric surgery for a variety of reasons, and in these circumstances the addition of

Table 38.1 Drugs used to manage obesity.

Drug name	Dosing	Mechanism of action	Expected weight loss	Common side effects
Semaglutide	2.4 mg weekly via SC injection	GLP-1 analogue ↑ Glucose sensitivity, satiety ↓ Gluconeogenesis, gastric emptying	−15.8% mean body weight change >10% weight loss in 70% of recipients	Nausea Diarrhoea
Liraglutide	3 mg OD via SC injection	GLP-1 analogue ↑ Glucose sensitivity, satiety ↓ Gluconeogenesis, gastric emptying	−6.4% mean body weight change >10% weight loss in 26% of recipients	Nausea Diarrhoea
Orlistat	120 mg TDS	Lipase inhibitor ↓ Absorption of dietary fat	−5% to 10% mean weight loss >5% weight loss in 52% of recipients	Diarrhoea Steatorrhoea
Naltrexone/bupropion	16 mg naltrexone /180 mg bupropion BD	Naltrexone: μ opioid receptor antagonist Bupropion: norepinephrine and dopamine reuptake inhibitor	−6.4% mean weight loss >10% weight loss in 28% of recipients	Nausea Headache Constipation
Phentermine/topiramate	7.5 mg phentermine/46 mg topiramate or 15/92 mg	Phentermine: centrally acting sympathomimetic Topiramate: anti-convulsant ↓ Appetite via hypothalamus	−10.9% weight loss from baseline >10% weight loss in 48% of recipients on high dose	Paraesthesia Dizziness Dry mouth Insomnia Constipation

BD, twice daily; GLP-1, glucagon-like peptide-1; OD, daily; SC, subcutaneous; TDS, thrice daily.

pharmacotherapy may be beneficial. The GRAVITAS study demonstrated the benefits of combining liraglutide with Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) for individuals with persistent or recurrent type 2 diabetes. Over the 26-week study period, 46% of the individuals in the liraglutide group lost >5% of their baseline body weight compared to 9% in the placebo group. Weight loss was also accompanied by improved HbA_{1c}, with 42% of the individuals in the treatment group reaching an HbA_{1c} <6.5% (48 mmol/mol) compared to 13% in the control group [32]. Although evidence for the use of pharmacotherapy in the postoperative period is limited to a relatively small number of studies, one study reported a greater response to the initiation of medications in those with a weight loss plateau rather than those who had regained weight [33].

Treatment cessation guidance is clearer for most newly approved anti-obesity medications in Europe and the USA. The European Medicines Agency (EMA) and US Food and Drug Administration (FDA) have provided *stopping rules* to identify individuals who are likely to be *responders* to any specific treatment [34]. Although there is some variability between different drugs, it is generally advisable that individuals should not be continue to take anti-obesity medications if they have lost <5% weight after 12 weeks at the full treatment dose. These guidelines are derived from studies that reported that early weight loss following initiation of a dietary or pharmacological intervention is strongly predictive of long-term outcomes [35, 36].

Bariatric surgery

The initial development of bariatric surgery originally stemmed from the observation that individuals undergoing surgical resection for upper gastrointestinal cancers frequently experienced profound and often problematic weight loss. This prompted the recognition that these same procedures could be used for individuals with obesity, making weight loss the primary indication rather than an unintended side effect of surgery. Critically, bariatric surgery not only provided clinically significant weight loss for individuals with obesity, but resulted in sustained weight loss in the long term.

Types of bariatric surgery

Since the early adoption of bariatric procedures, there have been dramatic developments not only from a technical standpoint in developing safer and highly effective procedures and approaches, but also from a mechanistic view, gaining a better understanding of the weight loss–dependent and independent physiological changes evoked by bariatric surgery and their long-term impact on obesity and related complications. Worldwide, more than 99.1% of primary bariatric procedures are now performed laparoscopically according to the latest IFSO Global Registry Report [37]. Refinement of techniques and the development of bariatric surgery are seen as a specialist area of practice, with morbidity and mortality rates now on a par with laparoscopic cholecystectomy and hysterectomy [38]. Although there is a growing body of level 1 evidence to support the efficacy of bariatric surgery in producing sustained long-term weight loss and resolution of comorbidity, no RCTs have demonstrated the superiority of one procedure over another; however, there are ongoing trials that may provide some clarity on this matter. Determining which procedure to perform should take into account individual comorbidities, the presence of obesity-related metabolic complications, potential short- and long-term risks of procedure-related complications, as well as the surgeon's experience.

Sleeve gastrectomy

Although a relatively new procedure, sleeve gastrectomy now accounts for 50% of all bariatric surgery, becoming the most commonly performed bariatric procedure worldwide [39]. Sleeve gastrectomy was originally one component of the two-stage duodenal switch procedure; however, once the substantial weight loss achieved was recognized, it was developed as a standalone procedure. The increased popularity of sleeve gastrectomy has been attributed in part to the perception that it is faster and less technically challenging to perform than traditional procedures, such as RYGB, while producing similar weight loss and resolution of comorbidity. Sleeve gastrectomy is associated with a significant reduction in ghrelin as a result of resection of the gastric fundus, along with post-prandial increases in GLP-1 and peptide tyrosine-tyrosine (PYY), which play important roles in appetite modulation and glucose homeostasis [39]. Sleeve gastrectomy may be associated with the development of new-onset or worsening of pre-existing reflux, which should be discussed preoperatively [40]. There is also concern regarding the development of Barrett's metaplasia as a result, and endoscopic surveillance in the postoperative period is now recommended one year postoperatively and every two to three years thereafter [41].

Adjustable gastric banding

There has been a dramatic reduction in the use of adjustable gastric banding, accounting for only 3.3% of all bariatric procedures in the 2021 IFSO Global Registry Report [37]. The fall in popularity is largely attributable to the view that it leads to a lesser degree of weight loss and resolution of obesity comorbidity compared to other widely available procedures, while being associated with a relatively high reintervention rate. Nevertheless, it can produce weight loss of ~20%, which is nearly equivalent to other bariatric procedures, although this requires close follow-up that may not be achievable in most healthcare settings [42, 43]. It is a relatively low-risk and reversible procedure and may still be considered in certain scenarios. Adjustable gastric banding may contribute to weight loss by promoting satiety during periods of fasting, likely mediated by vagal afferents [44].

Roux-en-Y gastric bypass

RYGB is a procedure that provides reliable weight loss and amelioration of obesity-related complications, particularly type 2 diabetes, with several RCTs supporting its use. It has decreased in popularity in recent years, in part due to its relative technical difficulty compared to sleeve gastrectomy, requiring the formation of two anastomoses. The mechanisms by which RYGB acts have been extensively investigated; it produces similar neurohormonal changes to sleeve gastrectomy, although perhaps with a more exaggerated response, with an increase in postprandial GLP-1 and PYY [45]. These changes have important effects on modifying the gut–brain axis controlling hunger, appetite, and satiety as well as mediating changes in bile acid metabolism [46]. In contrast to sleeve gastrectomy, which may produce worsening of reflux symptoms, RYGB is a treatment for people with obesity and reflux in its own right, and thus may be a more appropriate choice than sleeve gastrectomy in this specific context [47].

One anastomosis gastric bypass

One anastomosis gastric bypass (OAGB) has emerged as a simplified version of RYGB, involving the formation of a small gastric pouch and the anastomosis of a loop of jejunum to the stomach, forming a gastro-jejunostomy. Similar to RYGB, this procedure results in the bypass of the proximal small bowel; however, it does not require the formation of a second jejuno-jejunal anastomosis. An RCT with two-year follow-up demonstrated that it resulted in weight loss and resolution of type 2 diabetes that was non-inferior to RYGB [48]. In comparison to RYGB, there was a higher rate of nutritional complications as well as steatorrhea. Concerns have also been raised about the worsening of gastro-oesophageal reflux following OAGB in those with preoperative symptoms of reflux, as well as the development of *de novo* gastro-oesophageal reflux in people with a prior diagnosis of hiatus hernia [49]. Evidence to support its use is limited as it is a relatively new procedure, and longer-term studies are needed to determine if weight loss and metabolic improvements are sustained in the long term.

Biliopancreatic diversion and duodenal switch

Although biliopancreatic diversion and duodenal switch is recognized as the procedure that produces the greatest degree of weight loss and long-term remission of type 2 diabetes, it is infrequently performed. Following biliopancreatic diversion and duodenal switch, people may lose >70% excess weight, and a 10-year follow-up study has demonstrated a diabetes remission rate of 50% compared with 25% following RYGB [50,51]. In spite of these rather impressive outcomes, this procedure accounts for only a small fraction of all procedures due in part to the technical challenge, but also as a result of the increased risk of both short- and long-term complications. In comparison to all other bariatric procedures, biliopancreatic diversion and duodenal switch has the highest associated 30-day mortality and one-year complication rate, which are attributable to pulmonary embolism and anastomotic leak, respectively [52]. Much of the weight loss following biliopancreatic diversion and duodenal switch is secondary to the relatively long segment of small bowel bypassed and very short (80–100 cm) common channel; however, this is also responsible for many of the long-term complications of the procedure related to nutrient deficiencies. People need to have lifelong nutrient supplementation and close follow-up monitoring, but even despite this they may remain deficient. A proportion will be refractory to treatment and up to 10% require reoperation to correct the ongoing micronutrient deficiency [53,54]. Iron, vitamin B_1 and B_{12}, folate, and fat-soluble vitamin levels are particularly problematic. The importance of close follow-up should not be underestimated, as nutrient deficiency may lead to irreversible complications, including Wernicke's encephalopathy and neuropathy.

Efficacy of bariatric surgery

There is a strong evidence base supporting the efficacy of bariatric surgery. The Swedish Obese Subjects (SOS) study, a prospective cohort study, has demonstrated the remarkable durability of weight loss in individuals undergoing bariatric procedures. Over a follow-up period of 20 years, people undergoing bariatric surgery maintained a mean change in body weight of −18%, which showed only a minor increase from the lowest point of −23% at two years postoperatively [55,56]. When comparing the two most commonly performed procedures, sleeve gastrectomy and RYGB, RCTs have shown that although there was greater weight loss and change in body mass index (BMI) following RYGB, the difference was not statistically different [57,58]. Looking beyond weight loss, in comparison to matched individuals with obesity receiving usual care, there was a reduction in all-cause mortality, including that from cardiovascular events as well as certain forms of cancer [56].

Early perceptions of bariatric surgery as a procedure limited to weight loss alone have shifted as mechanistic studies have demonstrated that bariatric surgery has multisystem effects. The ability to reliably induce and maintain weight loss has provided a model to gain greater insight into and understanding of the impact of weight loss on obesity-related diseases, particularly type 2 diabetes. Through weight loss–dependent and –independent pathways, bariatric surgery results in the modification of several pathological processes driving the development of obesity, as well as reducing the risk of obesity-related complications. The rapid, metabolic changes induced by bariatric surgery are in part mediated by neurohormonal changes that result in rapid improvements in glycaemia in people with type 2 diabetes that are independent of weight loss. The findings from these mechanistic studies have been supported by more than 13 RCTs, which have consistently demonstrated the positive effects on glucose levels following bariatric surgery, irrespective of the procedure performed compared to medical treatment for type 2 diabetes and prior to the onset of weight loss [42,51,59–69]. As such, the second Diabetes Surgery Summit (DSS-II) developed guidelines that saw bariatric surgery as a key element in the treatment for type 2 diabetes in individuals with obesity. These recommendations have been endorsed by international governing bodies including the American Diabetes Association and the International Diabetes Federation as a central part of their management algorithms [70,71].

The adoption of a diabetes-focused model of care with metabolic surgery saw treatment targets being largely driven by improved glycaemic levels, with weight loss viewed as a secondary goal of treatment of lesser consequence. This view ignores the role of obesity in the underlying pathophysiology of type 2 diabetes, and studies have shown that bariatric surgery can modify several pathways contributing to the development of obesity. The modification of the gut–brain axis following bariatric surgery, altering the release of several critical gastrointestinal hormones implicated in the regulation of appetite and satiety, has been highlighted as of particular importance in mediating long-term weight loss maintenance by decreasing the symptoms of hunger associated with obesity. GLP-1 and PYY are both secreted primarily by L cells in the terminal ileum, and increased levels in the postoperative period have been implicated in the sustained weight loss produced following sleeve gastrectomy and RYGB [72]. Increased secretion of GLP-1 in the postoperative period is directly linked to the rapid improvements in glucose metabolism, but it also plays a role in appetite regulation. This effect is enhanced by PYY, a hypothalamic regulator of satiety that mediates decreased gastric acid secretion and delayed gastric emptying, both of which counteract some of the orexigenic effects mediated by falling leptin levels following bariatric surgery [73]. The alterations in gut hormones may also be potentiated by the anatomical bypass of the proximal small bowel, resulting in elevated plasma bile acids. Following RYGB, terminal ileal L cells are stimulated by the passage of undiluted bile acids, which produces a subsequent further increase in postprandial GLP-1 levels, contributing to increased satiety and weight loss maintenance in the postoperative period [46].

The improved glycaemic levels following bariatric surgery are related to both weight-independent mechanisms, such as alterations in neurohormonal signalling, and weight-dependent mechanisms. Although changes in the early postoperative period allowing rapid

improvements in glycaemic levels occur in a weight-independent manner, it is important to recognize the importance of weight loss in long-term control and remission. In conjunction with additional factors such as the duration of diabetes, age, and insulin use, the amount of weight lost in the postoperative period is a predictive factor in determining which individuals will sustain diabetes remission in the long term [74].

Long-term complications of bariatric surgery

Although bariatric surgery has consistently been demonstrated to be associated with low morbidity and mortality, there are recognized long-term sequelae. The specific complications and the likelihood of each are largely dependent on the procedure performed and the resultant anatomical and physiological changes.

Nutritional deficiencies

Long-term nutritional supplementation and close micronutrient monitoring are important for all people undergoing bariatric surgery, but particularly after biliopancreatic diversion and duodenal switch, given the higher risk of iron, folate, and fat-soluble vitamin deficiencies. These can lead to severe, irreversible complications such as Wernicke's encephalopathy and peripheral neuropathy. Even with supplementation, some may remain refractory to treatment and up to 10% will require reoperation due to nutrient deficiencies [53].

Metabolic bone disease

Following bariatric surgery, increased bone turnover and decreased bone mineral density coupled with micronutrient deficiencies, including vitamin D, contribute to a recognized increased risk of fracture [75]. The risk of both hip and wrist fractures appears to be higher following RYGB compared to sleeve gastrectomy or adjustable gastric banding; however, there was no increased risk compared to individuals with obesity [76,77]. The increased risk following RYGB highlights the importance of ongoing nutrient supplementation and monitoring.

Internal hernia

Sudden, severe-onset abdominal pain, nausea, or vomiting following RYGB or OAGB merits urgent investigation given the risk of internal herniation. Although the hernial defects are typically closed during both procedures, the loss of mesenteric fat in the postoperative period can result in an enlargement of the previously closed defect. Computed tomography (CT) scanning tends to show a typical swirling pattern, although studies have demonstrated that imaging is often falsely reassuring and diagnostic laparoscopy is recommended to definitively diagnose or rule out internal hernia [78,79].

Gallstone disease

There is an increased risk of developing gallstones following bariatric surgery due to the significant weight loss and alterations in enterohepatic circulation [80]; however, strategies such as concomitant laparoscopic cholecystectomy at the time of bariatric surgery are now rarely employed because of the increased risk of perioperative complications and prolonged hospital stay [81]. An RCT examining the use of prophylactic ursodeoxycholic acid in people with asymptomatic gallstone disease demonstrated no reduction in symptomatic gallstones following bariatric surgery [82]. Owing to the anatomical changes limiting access to the remnant stomach and duodenum, the management of gallstone disease with endoscopic retrograde cholangiopancreatography is more challenging following RYGB, but is still possible with surgical assistance if required.

Slipped gastric band

A slipped gastric band typically presents with upper abdominal or chest pain, nausea, and intolerance of oral intake. The underlying pathology is herniation of the distal stomach through the band with resultant proximal pouch dilatation [83]. Diagnosis can be made with an erect chest X-ray to quickly establish the band position, but a CT scan or oral contrast study may be more helpful. The initial management is band deflation, which should be done promptly to prevent ischaemia and necrosis. If the band cannot be deflated or symptoms continue, urgent surgical removal is required [84].

Bariatric surgery referral pathways

The referral pathways for bariatric surgery are largely based on the National Institutes of Health (NIH) guidelines issued in 1991, which have since formed the basis of most treatment guidelines. These recommendations are primarily guided by BMI, which is increasingly being recognized as a poor measure of the potential implications of obesity; however, it remains central to the decision-making process, in part due to pragmatic reasons [85]. There is an increasing focus on offering early intervention in those with obesity-related complications, particularly type 2 diabetes, in recognition of their impact on mortality, morbidity, and quality of life. The National Institute for Health and Care Excellence (NICE) recommendations for bariatric surgery according to BMI are shown in Table 38.2.

Referral pathways to weight management services vary, but generally follow a tiered approach, involving multidisciplinary team care. The tier system presents a means of offering structured treatment intensification with an increased level of support from members of the multidisciplinary team, including psychologists, dieticians, specialist nurses, endocrinologists, and surgeons. Involvement of the multidisciplinary team with a specialist weight management service is central to the delivery of personalized care and improves weight loss outcomes [86]. The tier system used in the UK National Health Service (NHS) is shown in Figure 38.1.

- Tier 1: primary care with community advice on weight loss measures.
- Tier 2: primary care with community interventions including dietary and exercise advice. Services may be delivered in a group setting.
- Tier 3: clinician-led (physician or GP with specialist interest in weight loss) multidisciplinary team to provide intensive weight loss support and advice, including a specialist nurse, specialist dietician,

Table 38.2 National Institute for Health and Care Excellence (NICE) recommendations for bariatric surgery according to body mass index (BMI) thresholds.

BMI threshold	Recommendation
>50 kg/m^2	Bariatric surgery should be considered as first-line treatment over lifestyle intervention or pharmacotherapy
>40 kg/m^2 or 35–39.9 kg/m^2 (with obesity-related comorbidity)	Bariatric surgery should be considered if lifestyle intervention and pharmacotherapy ineffective
30–34.9 kg/m^2	Bariatric surgery should be considered if there is a diagnosis of type 2 diabetes in the past 10 yr
27.5–29.9 kg/m^2	Bariatric surgery should be considered in people of Asian origin with recent onset of type 2 diabetes

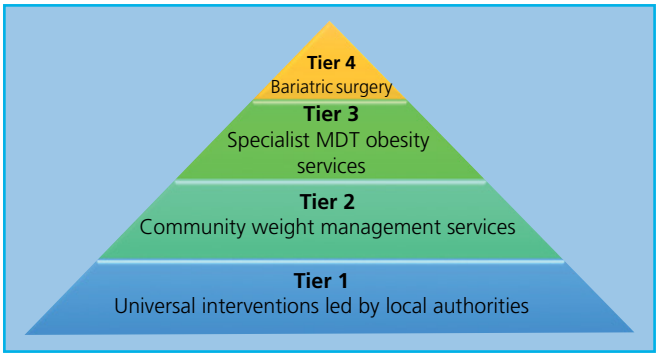

Figure 38.1 UK National Health Service tiered system for obesity care. MDT, multidisciplinary team.

psychologist, and physiotherapist. These services should be offered on a 1 : 1 basis.

- Tier 4: referral to obesity services for consideration for bariatric surgery.

Alternative pathways to manage obesity have been proposed to adopt a more flexible, personalized approach to care. Although the multidisciplinary team remains central to its delivery, a simplified two-tier system comprising a prevention and a treatment tier may allow for the delivery of treatment most appropriate for the individual rather than requiring a mandatory stepped approach [87].

Conclusion

Although weight loss in itself presents a challenge for many individuals, what remains the most important element of obesity management for the purposes of health benefit is the period of weight loss maintenance. As illustrated by the Look AHEAD trial, this remains challenging with diet and lifestyle changes alone despite an initial period of weight loss. Weight loss interventions also tend to result in a lesser degree of weight loss in people with type 2 diabetes compared to those without, although the exact mechanisms responsible for this have not been elucidated. Having recognized the importance of glycaemic levels in individuals with type 2 diabetes, there has been a move away from weight-based treatment targets. It is increasingly acknowledged that weight loss is an important metric in its own right. Treatments aimed at weight loss and particularly those that mediate long-term weight loss maintenance modify the underlying disease processes related to obesity and may produce improvements in both morbidity and mortality associated with type 2 diabetes.

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39 In-Hospital Treatment and Surgery in People with Diabetes

Ketan Dhatariya[1], Philip Newland-Jones[2], and Mayank Patel[2]

[1] Norfolk and Norwich University Hospitals NHS Foundation Trust and University of East Anglia, Norwich, UK

[2] University Hospitals Southampton NHS Foundation Trust, Southampton, UK

Key points

- The number of people with diabetes in hospital continues to increase.
- Hyperglycaemia (particularly in those people not known to have diabetes prior to hospital admission or those experiencing stress hyperglycaemia) and hypoglycaemia are associated with increased levels of harm, defined using whatever measure is chosen.
- Levels of knowledge about diabetes among healthcare staff remain inadequate and levels of satisfaction about inpatient diabetes care remain low.
- The role and early involvement of a diabetes inpatient specialist team are stressed as an important factor in the education of people with diabetes and staff.
- Several national and international guidelines are now available to help teams manage this increasingly complex cohort of patients, and aim to achieve suitable glycaemic levels that avoid symptomatic hyperglycaemia or debilitating hypoglycaemia.
- The lack of robust data means that the target glucose concentrations for hospitalized individuals with diabetes have yet to be clearly determined.

Known diabetes in hospital

The prevalence of diabetes in the general population of Western Europe is approximately 6–7%, and is expected to rise significantly over the next 20–30 years [1]. The prevalence of diabetes in other parts of the world is much higher; in North America and the Caribbean it is reported to be between 10.5% and 11.1% overall, with some counties of the USA having a prevalence of 33% [1, 2]. Having diabetes more than doubles the risk of being hospitalized for any given condition [3], which is reflected in the high prevalence of diabetes in hospitals. Data from the 2019 UK National Diabetes Inpatient Audit (NaDIA) showed that the prevalence of people with diabetes in hospital ranged from 8.3% to 31%, with a mean of 18.1% [4]. People with diabetes have a longer length of hospital stay and higher mortality rates than those without the condition [5]. This translates to greater costs; in the UK in 2010, it was estimated that diabetes accounted for over 10% of the entire budget of the National Health Service (NHS), with the excess costs of people with diabetes in hospital equating to between £573 million and £686 million per annum [6]. In the USA, data suggest that in 2017, 25% of the health budget was spent on diabetes, equating to $327 billion, a rise of 25% (after adjusting for inflation) from 2012 [7, 8].

Undiagnosed diabetes and stress hyperglycaemia in hospital

Aside from those with known diabetes prior to hospital admission, many people with hyperglycaemia are admitted without a prior diagnosis of diabetes. These include those with previously unknown diabetes but who continue to have hyperglycaemia after discharge. However, some people may develop transient hyperglycaemia during their inpatient stay that normalizes after discharge, so-called *stress hyperglycaemia* [9, 10]. The glucose values that represent stress hyperglycaemia vary, with some suggesting a fasting glucose level of ≥7.0 mmol/l (126 mg/dl) or a random blood glucose level of >11.1 mmol/l (200 mg/dl) [10], while the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) more recently defined it as any glucose level >7.8 mmol/l (140 mg/dl) in an individual without a prior diagnosis of diabetes [3, 11]. Taken together, the number of people in hospital with either diabetes or transient hyperglycaemia is significant, with a prevalence of between 32% and 38% on general wards [12, 13] and between 28% and 80% of those with critical illness or undergoing cardiac surgery [13–17].

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Pathophysiology of hyperglycaemia in acute illness

In fasting healthy individuals, glucose levels are usually maintained between 3.9 and 5.6 mmol/l (70 and 100 mg/dl). Glucose concentrations are finely controlled to match endogenous glucose production from the liver (with approximately 20% of the total coming from the kidneys) and glucose utilization by peripheral tissues [18–21]. The glucose concentrations are controlled by the balance of insulin and the counter-regulatory hormones, glucagon, catecholamines, growth hormone, and cortisol. At relatively low concentrations, insulin is a potent inhibitor of lipolysis, free fatty acid oxidation, and ketogenesis. As insulin concentrations increase, it lowers glucose concentrations, first by inhibiting hepatic gluconeogenesis and glycogenolysis, and then increasing peripheral glucose uptake and promoting glycogen synthesis. At even higher concentrations, insulin prevents protein breakdown and finally, at the highest concentrations, insulin acts to promote skeletal muscle formation [22, 23].

Hyperglycaemia develops as a result of an imbalance between the glucose-lowering effect of insulin and the glucose-raising counter-regulatory response. Hyperglycaemia occurs as a result of (i) increased gluconeogenesis; (ii) accelerated glycogenolysis; and (iii) impaired glucose uptake and utilization in peripheral tissues [24]. The first two of these constitute the major contribution to hyperglycaemia. Skeletal muscle breakdown leads to an increased delivery of gluconeogenic precursors in the form of amino acids. Fat breakdown leads to an increased quantity of free fatty acids delivered to the liver. These effects may be exacerbated by prolonged starvation or during the fasting needed in the perioperative period [25]. In people without diabetes, a compensatory increase in insulin secretion helps to mediate against these catabolic effects. Without the glucose-lowering effects of insulin, the activity of gluconeogenic enzymes, in particular phosphoenolpyruvate carboxykinase, fructose-1,6-bisphosphatase, and pyruvate carboxylase, is increased [20, 26]. During times of illness or stress, the increased concentrations of counter-regulatory hormones alter carbohydrate metabolism by inducing insulin resistance, increasing hepatic glucose production, and reducing peripheral glucose utilization [9, 10]. A major consequence of severe hyperglycaemia is an osmotic diuresis that, if not countered, leads to dehydration and electrolyte disturbances, due to urinary loss of sodium, potassium, magnesium, and phosphate. The resulting increased plasma osmolality leads to a pro-coagulant state. In addition, hyperglycaemia results in raised concentrations of inflammatory cytokines and markers of oxidative stress such as tumour necrosis factor α, interleukin (IL)-6, IL-1β, IL-8, and C-reactive protein [27–30]. These pro-inflammatory cytokines are associated with the development of insulin resistance by interfering with intracellular pathways downstream of the insulin receptor [27, 29, 31–34]. Furthermore, inflammatory cytokine concentrations fall when the glucose returns to normal [29].

There are other causes of hyperglycaemia that may be more specifically related to hospital admission [35]. These include co-administered medications such as enteral or parenteral nutrition, vasopressors, or corticosteroids. Almost 13% of all people in hospital were receiving corticosteroids, of whom 13% had a prior diagnosis of diabetes [36]. However, despite corticosteroid use being a cause of hyperglycaemia, which is associated with harm, only 20.8% of those on corticosteroids were having glucose monitoring [36]. In a recent study of people admitted with inflammatory bowel disease and treated with steroids, 60% had a recorded episode of hyperglycaemia, including 57% who did not have a diagnosis of diabetes [37]. This issue is likely to become of greater concern with the evidence that corticosteroid use, in particular dexamethasone, reduces mortality in those admitted with moderate SARS-CoV-2 infection treated with oxygen therapy [38–42]. People with diabetes are at increased risk of being hospitalized with SARS-CoV-2 and their outcomes are worse than those without hyperglycaemia or diabetes [43–46]. Guidelines from the Joint British Diabetes Societies (JBDS) Inpatient Care Group in the UK and Diabetes UK are available to help tackle the management of hyperglycaemia and diabetes for those with or without Covid-19 infection [47, 48].

Evidence of harm from in-hospital hyperglycaemia and effect of glucose lowering

Prior to the publication of large, randomized controlled trials in the 1990s, it had been well recognized that suboptimal diabetes management in ambulatory people with either type 1 diabetes or type 2 diabetes was associated with worse outcomes. The Diabetes Control and Complications Trial [49] and UK Prospective Diabetes Study [50] showed that interventions to improve glycaemic levels maintained over many years were associated with improved outcomes. In the world of hospitalized individuals with diabetes, there is compelling evidence that high blood glucose concentrations are associated with higher in-hospital morbidity and mortality, prolonged length of stay, unfavourable post-discharge outcomes, and significant excess healthcare costs in medical and surgical specialties [2, 12, 51–54]. Umpierrez et al. showed that individuals with new-onset hyperglycaemia had a striking 18-fold increase in in-hospital mortality, whereas people with known diabetes had a 2.7-fold increase in in-hospital mortality, compared with people with normoglycaemia [12]. In 2004, a joint position statement from the American College of Endocrinology (ACE) and the AACE on hospitalized individuals with diabetes and metabolic management concluded that hyperglycaemia in hospitalized individuals is a common, serious, and costly healthcare problem. There was a strong recommendation for early detection of hyperglycaemia and an aggressive management approach to improve outcomes [3]. In the UK, the JBDS has produced a series of guidelines on managing various aspects of diabetes care during hospital admission, which also recommend aggressive glucose management [48].

Hyperglycaemia, measured by glucose or glycated haemoglobin (HbA_{1c}), in the perioperative period is associated with poor outcomes in several surgical specialties, most often in those not previously known to have diabetes [53–59]. These poor outcomes include longer length of hospital stay and time in the intensive care unit (ICU), development of urinary tract and surgical site infections, and mortality. The reasons for these adverse outcomes are multifactorial, but include failure to identify those with diabetes and/or hyperglycaemia [60]; multiple comorbidities, including microvascular and macrovascular complications [61–67]; complex polypharmacy and insulin prescribing errors [68]; increased perioperative and postoperative infections [54, 69, 70]; associated hypoglycaemia and hyperglycaemia [54]; lack of or inadequate institutional guidelines for management of diabetes and/or hyperglycaemia during the admission [54, 71]; and inadequate knowledge of diabetes and hyperglycaemia management among staff delivering care [72–74].

Having a diagnosis of diabetes prior to surgery is associated with a lowering of risk despite the hyperglycaemia [53, 54, 75], implying that the knowledge of diabetes is protective. It may be that people with diabetes have more attention paid to them, and thus have more contact with nursing and medical staff, which may mean that postoperative problems are picked up sooner [75]. What remains to be determined is whether it is the hyperglycaemia *per se* that causes the increased harm, or whether the high glucose is a marker for underlying disease severity.

While it is well established that perioperative hyperglycaemia is associated with harm, the association between high preoperative HbA_{1c} and outcomes is uncertain [76] because of a lack of high-quality prospective observational studies examining the relationship between HbA_{1c} and postoperative morbidity and mortality. The risks appear to increase when preoperative HbA_{1c} is >64 mmol/mol (8%), leading the UK JBDS guidelines to recommend a preoperative level of <69 mmol/mol (8.5%) [55].

There are increasing data, particularly from surgical specialties, to suggest that achieving optimal glycaemic levels during hospitalization is associated with improved outcomes [77, 78]. It was therefore surprising to see that the UK National Institute for Health and Care Excellence (NICE) suggest that there was little evidence to show that tight glucose management improves postsurgical outcomes in people with type 2 diabetes, or those not known to have diabetes, and that 'tight blood glucose control is not necessary for people in these two groups', although this likely represents the high level of evidence required by NICE to make solid recommendations [79]. For people with type 1 diabetes in the hospital, NICE recommends aiming for a blood glucose target of between 5.0 and 8.0 mmol/l [80]. Glycaemic targets are discussed in more detail in the next section.

Glycaemic targets for individuals with diabetes in hospital

The threshold for diagnosing hyperglycaemia during admission to hospital has been suggested as a random glucose >7.8 mmol/l (140 mg/dl) [11, 81]. In addition, it has been recognised that hypoglycaemia (i.e. blood glucose <4.0 mmol/l; 72 mg/dl) is associated with increased morbidity and mortality [82–84]. Hypoglycaemia is usually related to pre-existing comorbidities and the severity of intercurrent illness, rather than to medication use [85]. To reduce the impact of hypoglycaemia, there is a general consensus that glucose concentrations should not be allowed to fall below this threshold, although there are arguments that even 4.0 mmol/l is too low [86]. However, until recently the lack of robust data showing that aggressive glucose lowering reduces the excess morbidity and mortality associated with hyperglycaemia has meant that it has been difficult to reach an agreed consensus on what the target glucose concentrations should be in people with diabetes. Different targets have been suggested for different categories of inpatients, for instance those in the ICU compared with those on a general ward, or those due to undergo surgery.

Intensive care unit

A significant amount of work has been undertaken to establish the optimal glycaemic levels that are associated with the lowest morbidity and mortality since the first study published in 2001 on individuals in the surgical ICU in Belgium [17]. That study compared outcomes in over 1500 inpatients randomized to a group given *usual care* – that is, glucose concentrations maintained between 10.0 and 11.1 mmol/l (180–200 mg/dl) – or treated with *intensive insulin therapy*, with glucose concentrations maintained between 4.4 and 6.1 mmol/l (80–110 mg/dl) and intravenous insulin given using an infusion pump. The mean glucose concentration in the usual care group was 8.5 mmol/l (153 mg/dl) and the mean concentration in the intensively treated arm was 5.7 mmol/l (103 mg/dl). Those randomized to the intensive insulin group did significantly better in all outcomes [17]. In particular, their mortality was reduced by 34%, but other outcome measures were also significantly improved, including less bacteraemia, less antibiotic use, shorter length of time on a ventilator, and fewer days in the ICU [17]. The authors then repeated the study in a medical ICU, with a mean glucose concentration in the intensively treated arm of 6.2 mmol/l (111 mg/dl), and showed that intensive insulin therapy was associated with a reduction in overall morbidity and a reduction in mortality if the stay on the ICU was over three days [83]. As a result of these two seminal studies, it had been suggested that the target for this cohort of inpatients should be between 4.4 and 6.1 mmol/l (80 and 110 mg/dl). However, subsequent attempts to reproduce these findings proved inconclusive, with most similar studies being unable to achieve similar reductions in morbidity or mortality [87–91]. Some of these subsequent studies were stopped early because of the significantly increased risk of harm due to the high frequency of severe hypoglycaemia [88–90].

In view of these and other findings, different recommendations have been published. A joint statement from the ADA and the AACE in 2014 recommended specific glycaemic targets in the ICU. They advocated for insulin initiation when glucose concentrations are persistently greater than 10.0 mmol/l (180 mg/dl), aiming for a glucose concentration between 7.8 and 10.0 mmol/l (140 and 180 mg/dl) [92]. They also suggested that in those centres with more experience in glucose management, a lower target of 6.1–7.8 mmol/l (110–140 mg/dl) may be appropriate provided that there is no increase in the incidence of severe hypoglycaemia [92]. By contrast, the Society of Critical Care Medicine in the USA recommends that glucose-lowering therapy is initiated once glucose levels rise above 8.3 mmol/l (150 mg/dl), and glucose concentrations should not be allowed to rise above 10.0 mmol/l (180 mg/dl) or drop below 3.9 mmol/l (70 mg/dl) [93]. Others have suggested that glycaemic targets vary according to a known or unknown diagnosis of diabetes [94], while there have been concerns that tight glycaemic management in critically ill individuals may do more harm than good [95].

A review of the literature on glucose levels in the ICU showed that there remained a wide variation in recommended targets, as well as methods to achieve them [96]. Of more concern, however, was a Chinese study reporting that many physicians did not know that hypoglycaemia in the people under their care was associated with harm, showing that more education was needed [97]. In summary, the issue of glycaemic targets in the ICU has yet to be resolved.

General wards

Studies from a variety of specialties show that hyperglycaemia in people in hospital is associated with negative outcomes [52, 98–101]; however, there is a paucity of good-quality data to inform the ideal targets for blood glucose in general wards. Until relatively recently, there were few data showing that optimizing glycaemic levels reduces the excess morbidity and mortality seen in hospital. Data are now emerging from surgical settings to show that achieving a glucose concentration of <8.3 mmol/l (150 mg/dl) is associated with

a lower risk of developing surgical site infection [78]. In the UK, the JBDS has published a series of consensus-based guidelines on several aspects of care for this increasingly large cohort [48]. It advocates that the target glucose concentration should be between 6.0 and 10.0 mmol/l (108 and 180 mg/dl), with a concentration of 4.0–12.0 mmol/l (72–216 mg/dl) being acceptable for medical patients and for conscious surgical patients, although the lower target of 4.0 mmol/l has recently been challenged [86]. The levels advocated by the JBDS are at slight variance with the USA, where the guidelines suggest targets for fasting glucose concentrations of <7.8 mmol/l (140 mg/dl) and a random glucose target of <10.0 mmol/l (180 mg/dl) [81]. Targets for those who are at the end of life are more relaxed (Chapter 73), aiming at avoiding symptomatic hypoglycaemia or hyperglycaemia, with concentrations of 6.0–15.0 mmol/l (108–270 mg/dl) being advocated in the UK [102] and similar but slightly lower levels in the USA [11].

Current recommended standards of hospital care for people with diabetes

Data from the USA in 2017 indicated that 38.7% of hospital bed days, accounting for an estimated 62.9 million days, were either attributable to or incurred by people with diabetes [7]. In the UK in 2019 people with diabetes occupied between 8.3% and 31% (mean 18.1%) of hospital beds [4]. Previous work from NaDIA and elsewhere has shown that the majority of people with diabetes were admitted for reasons other than diabetes, with ~90% admitted as an emergency [2, 103]. In addition, one in four people admitted with heart failure, heart attack, or stroke has diabetes [2].

Professional organizations from different countries publish recommended standards of hospital care. The International Diabetes Federation (IDF), an umbrella organization of more than 200 national diabetes associations in over 160 countries, offers a broad perspective on care relating to people with type 1 diabetes and type 2 diabetes during hospitalization, but acknowledges that not all countries have the infrastructure or resources to offer the same care standard for all. It therefore offers three care categories – recommended care, limited care, and comprehensive care – to which member organizations can benchmark [104, 105]:

- *Recommended care*. This is evidence-based care that is cost-effective in most nations with a well-developed service base, and with healthcare funding systems consuming a significant part of national wealth. Recommended care should be available to all people with diabetes and the aim of any healthcare system should be to achieve this level of care. However, as there are considerable variations in resources throughout the world, other levels of care are described that acknowledge low- and high-resource situations.
- *Limited care*. This is the lowest level of care that anyone with diabetes should receive, as standard medical resources and fully trained health professionals are often unavailable in poorly funded healthcare systems. However, even with limited and cost-effective resources, this level of care aims to achieve a high proportion of what can be achieved by recommended care. Only low-cost or high cost-effectiveness interventions are included at this level.
- *Comprehensive care*. This level of care includes the most up-to-date and complete range of health technologies that can be offered to people with diabetes, with the aim of achieving the best possible outcomes. However, the evidence base supporting the use of some of these expensive or new technologies is relatively weak.

Similar themes emerge when reviewing these documents relating to care, including the following:

- A diabetes diagnosis should be clearly identified in the hospital medical case records.
- All people with diabetes admitted to hospital should have their blood glucose level and HbA_{1c} measured, with results available to all members of the healthcare team.
- There should be an emphasis on insulin safety, particularly when using intravenous insulin infusion.
- Recommended blood glucose targets for people with diabetes in hospital should be stated, thereby reducing the risk of hypoglycaemia and hyperglycaemia.
- Discharge planning should be implemented on admission to hospital.
- Systems and policies should be in place that recognize the specific needs of people with diabetes in hospital.
- Each hospital should identify a clinical lead for inpatient care for people with diabetes.
- All people with diabetes should have access to a specialist inpatient multidisciplinary diabetes team.
- Staff caring for people with diabetes should be appropriately trained and competent in the management of inpatient diabetes.
- Diabetes self-management should be integrated into usual ward care.

Because of the ageing population, there are specific needs that also need to be considered. These are dealt with in more detail elsewhere [104, 106] (Chapter 72).

Minimizing length of stay

Reducing excess hospital length of stay is one of the principal aims of good care. Prolonged length of stay may occur for a multiplicity of reasons, but is often because of diabetes mismanagement secondary to inadequate staff knowledge and lack of education [72–74]. Insulin errors are associated with a longer hospital stay, and although it is recognized that certified diabetes educators (CDEs) and diabetes specialist nurses (DSNs) are effective in reducing length of stay, the majority of people with diabetes do not come into contact with these healthcare professionals during admission [107, 108]. The IDF and the ADA, as well as the JBDS in the UK, are among many organizations that have put discharge planning as a priority at the time of admission and not as an afterthought just prior to discharge [81, 109, 110]. Intervention by the diabetes inpatient team reduces the incidence of hypoglycaemia, reduces length of stay, and prevents 30-day readmission [111]. One systematic review and meta-analysis showed that reducing hypoglycaemia rates reduced length of stay by over four days [112].

Discharge planning defines the agreed management plan for that episode of care, including assessment and prompt referral to the specialist team if necessary, and can aid in anticipating and therefore preventing problems. When possible, this planning should be done in collaboration with the person with diabetes.

Patient safety

The issues surrounding inpatient safety focus predominantly on insulin and diabetes management errors, as well as the risks of infection or debilitation associated with extended length of hospital stay. Globally, insulin is one of the five highest-risk medications [113]. One-third of all hospital medical errors that cause death within 48 hours of the error involve insulin administration. Insulin medication errors can occur at any stage in the process of prescribing, preparing, and delivering the medication [114]. Errors

involving insulin infusion have been highlighted particularly in the last few years [103, 115]. In the UK, the 2019 NaDIA showed that 37.2% of those in hospital with type 1 diabetes and 40.3% of those with type 2 diabetes experienced an insulin-related drug error [4].

The UK National Patient Safety Agency reviews all medication errors, including those relating to insulin. In 2010, it published a six-year audit of reported insulin errors described as moderate and severe; 3881 reports were received and these included inpatient deaths [114]. It is well recognized that insulin errors occur because of the medication's complexity and its narrow therapeutic window. Initiatives to improve insulin prescribing and reduce these risks [116] include the introduction of electronic prescribing, while specialist diabetes pharmacists have been associated with lower error rates [117].

The use of sodium–glucose co transporter 2 (SGLT-2) inhibitors is beneficial for those with heart failure, and delays the progression of renal disease [118–124]. However, they increase the risk of dehydration, worsening renal function, and genital yeast infections. There is also a low but significant risk of developing euglycaemic or hyperglycaemic diabetic ketoacidosis (DKA). Although there are few data to support routine use of SGLT-2 inhibitors in the acute setting, if a person is already taking them prescribers should remain cautious, with a low threshold for temporarily discontinuing them [125].

Diabetes self-management

When not in hospital, people with diabetes are accustomed to managing their own condition. Traditionally, people with diabetes are disempowered in the management of their diabetes as soon as they are admitted, and for many this disempowerment is a negative experience [109, 126, 127]. The IDF has promoted the need for individuals to be enabled to self-manage their own condition [109]. Self-management includes the whole process of adjusting insulin treatment in response to self-measured glucose values [128]. The USA and UK have also set national standards defining the principles of self-management of diabetes, but there is general acceptance that there is no best practice education programme that meets the needs of all people with diabetes [129, 130].

Although this is an institutional decision, in principle individuals with diabetes in hospital should be given the opportunity to decide whether they wish to self-manage their condition during their admission, provided that they are well enough to do so. The key principle of self-management is that the person with diabetes has primary responsibility for making the decision about whether they should self-manage their own diabetes. Individuals suitable for self-management in hospital must be competent adults with a stable level of consciousness who successfully manage their diabetes at home. In addition, while in hospital it is advised that these people have the physical skills appropriate to self-administer insulin, be accustomed to performing glucose monitoring, and have adequate oral intake. In the event that self-care is deemed unsafe or impossible (e.g. critically ill, post-surgery, or unwillingness to self-manage), there must be a governance arrangement to assess their competency and, if necessary, supersede the individual's right to self-care. Hospitals should have a person-centred policy for diabetes self-management. Encouraging and supporting individuals to take as much responsibility for their diabetes management as they wish, and their clinical status allows, are likely to enhance the experience during a hospital stay [128, 131]. Part of this involves institutions providing written information for staff and patients to explain the responsibilities of self-management. For elective surgical patients, this written information may be provided at the time of the pre-assessment clinic. In addition, for elective admissions, a care plan should be agreed at that time to establish whether the person with diabetes wishes to self-manage and the circumstances in which this may not be possible [128].

At the time of admission, the responsible nurse and the person with diabetes should again agree on the circumstances in which the individual with diabetes should or should not self-manage. Ideally, an agreement form should be signed by both the person with diabetes and the responsible nurse. People with diabetes should be able to monitor their glucose with their own glucose monitoring equipment, but results should be made available to hospital staff. For hospitals that utilize centrally uploaded glucose monitors, it is useful to maintain some monitoring on hospital equipment to allow system safety netting to continue. In addition, the technique for glucose testing and insulin administration should also be assessed. Once the person with diabetes has administered their own insulin, the dose self-administered should be recorded on the prescription chart, or an entry made on an electronic prescription by a member of staff.

To allow people with diabetes to keep and administer their own insulin, facilities should be available for safe storage of insulin and disposal of sharps in the ward environment. In addition, the institution should ensure that the timing and content of meals are suitable for people with diabetes; this is a common cause of unhappiness and dissatisfaction among those with diabetes [132].

It is important that clinical circumstances be regularly assessed during the admission to ensure that the individual's ability to self-manage has not been compromised by their clinical condition. If there are doubts or disagreements between the person with diabetes and the staff as to whether they can self-manage, then the diabetes specialist team may need to be involved.

Patient satisfaction

The experience of people with diabetes in hospital is important and plays a crucial role when developing local and national guidelines, but there is little in the worldwide literature evaluating experience during hospitalization. The UK has, however, gathered a large amount of information on patient satisfaction through two sources.

The Diabetes Inpatient Satisfaction Study was a cross-sectional study carried out in the UK measuring diabetes treatment satisfaction and its relationship to diabetes care in hospital by the validated Diabetes Treatment Satisfaction Questionnaire for Inpatients in over 1300 people with insulin-treated diabetes [132, 133]. Satisfaction with the general diabetes treatment was high, but there were high levels of extreme dissatisfaction with meal choices and quality, and lack of similarity of hospital meals to normal domestic choices: 23% would never or rarely have made similar meal choices at home.

Hyperglycaemia or hypoglycaemia was reported for much of the hospital stay (20% and 7%, respectively) and 26% reported at least one severe hypoglycaemic episode. More frequent hyperglycaemia or hypoglycaemia was associated with significantly poorer overall satisfaction scores and negative well-being scores and lower satisfaction with the timing of medication in relation to meals. Factors that were significantly associated with the highest levels of satisfaction were the amount of time spent with a diabetes inpatient specialist nurse (DISN) and insulin self-administration [132].

Satisfaction questionnaires were an integral part of NaDIA, which has run over several years [4]. The 2019 audit showed a wide variation in satisfaction scores between institutions, but a consistent finding was that the patient experience had worsened since

2011 in terms of meal choice, meal timing, and the individuals' perception of the knowledge of diabetes among the staff caring for them [4].

The role of the diabetes specialist team

The person with diabetes remains at the heart of the specialist team. Diabetes specialist inpatient teams are multidisciplinary and should include a consultant in diabetes with a specialist interest in inpatient care, who often is seen as the lead, working closely with DISNs or CDEs, diabetes dieticians, pharmacists, and specialist podiatrists. Extended foot team members should include orthopaedic and vascular surgeons, microbiologists, tissue viability nurses, and interventional radiologists. When necessary, rehabilitation teams should also be available. The specialist team should work together by individually contributing their specialist skills to provide a holistic approach to patient care. The success of such teamwork requires a culture that invests in excellent communication between the person with diabetes, diabetes specialists, and non-specialist teams to activate timely intervention to prevent glycaemic deterioration during the hospital stay.

Involvement of the specialist diabetes team, and in particular DISNs and CDEs, significantly reduces length of stay and insulin errors and improves the patient experience, while reducing readmissions [6, 107, 135–136].

A CDE is a health professional in North America who possesses comprehensive knowledge of and experience in diabetes management. Unlike the DISN in the UK, the role is not exclusive to nursing, but CDEs must have a relevant health-related degree and undergo extensive training. Both CDEs and DISNs educate and support people affected by diabetes to understand and manage the condition and promote self-management to achieve individualized behavioural and treatment goals that optimize health outcomes. Working in close partnership with people in the community, such as social workers, case managers, and home care coordinators, they are able to facilitate a smooth care pathway from hospital to home at discharge. The DSNs, who work exclusively in diabetes care, and the CDEs are also integral to providing ongoing staff training and may also be prescribers [107]. Aside from clinical care, they are frequently involved in medical and nursing education. Despite these numerous attributes, the 2019 NaDIA showed that almost one-fifth of UK hospitals do not have a DISN, while the number of hospitals offering inpatient dietetic or podiatry support is even worse [4].

Staff education

One of the key roles for the diabetes inpatient team is to educate ward-based non-specialist healthcare professionals and others, including paramedical, nursing, and medical students. Ward staff may have little or no protected time for education and training other than mandatory training defined by the employing organization. Despite the large numbers of people with diabetes in hospital, often the only mandatory training in diabetes is in blood glucose monitoring. People with diabetes, who may have a high level of knowledge about their condition, are therefore frequently managed by nursing and medical staff who only have a rudimentary knowledge and training in diabetes care [72–74, 137]. Hence it is the senior physicians who have the responsibility for educating junior medical staff, while the CDE and DISN teams are often best placed to offer education to ward-based staff because they can use the opportunity when reviewing patients to provide education to other non-specialist staff. Utilizing multiple professional groups, including medical, nursing, and pharmacy staff, to provide consistent safety messages to all professions will help to maximize the impact of education in a hospital setting.

Because so many people in hospital have diabetes, it is almost impossible for specialist team members to see every person on a regular basis. In the UK, specialist teams therefore have drawn up a priority list of those who should be referred for assessment (Figure 39.1); this can be adapted based on local need. Ward-based and specialist nursing staff in the UK have to undergo a revalidation process that includes ascertaining the views of the person with diabetes and demonstrating competency [137, 138].

Management of in-hospital hyperglycaemia

The ADA has stated that it is incumbent on organizations to ensure that diabetes is appropriately managed in hospital [81]. This sentiment is similar to one echoed by the now decommissioned NHS Institute for Innovation and Improvement in the UK, which said that it is as unacceptable for hospitals not to have a glycaemic management policy as it is for them not to have an infection control policy.

People with diabetes occupy a significant proportion of hospital beds, with one in six in the UK and about one in four in the USA [4, 7]. This does not include those who develop raised

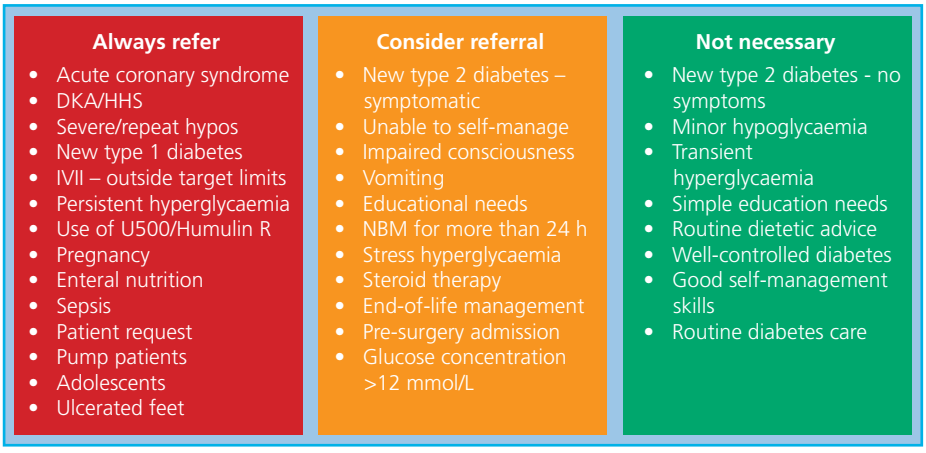

Figure 39.1 Prioritization of those who should be seen by a specialist diabetes inpatient team. DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycaemic syndrome; IVII, intravenous insulin infusion; NBM, nil by mouth. Source: Adapted from ThinkGlucose.

glucose concentrations due to stress hyperglycaemia [10, 139]. The majority of people with diabetes are not admitted to hospital to address and treat complications associated with the diabetes. Management of blood glucose often becomes secondary to the care of the primary diagnosis requiring admission. In people without diabetes who develop dysglycaemia during an acute illness, high or low glucose levels are often ignored or treated inappropriately. Poor glycaemic management is common for many reasons [103]. Over the last decade or more, the issue of inpatient diabetes has become a higher priority, with the UK JBDS Inpatient Care Group producing different guidelines addressing various issues surrounding inpatient glycaemic management [48]. In the USA, the Partnership to Improve Diabetes Education (PRIDE) group was set up to address inpatient glycaemic management [140].

Medication to manage in-hospital hyperglycaemia

Because of the risks of ineffectiveness, the potential for drug-related side effects and toxicity, and the risk of hypoglycaemia, until recently oral agents had not been recommended for the management of hyperglycaemia in hospital [3, 11, 141]. Commonly, oral medication was stopped and intravenous insulin substituted because it provided the greatest flexibility in the hospital setting to achieve optimal blood glucose levels. However, it is increasingly recognized that the use of insulin and insulin secretagogues is associated with the development of severe hypoglycaemia [76, 142]. In addition, over the last 10 years studies have shown that some of the newer agents are safe within the hospital setting, leading to a change in recommendations. For those admitted to general medical and surgical wards or older people, appropriate oral medication, particularly dipeptidyl peptidase 4 (DPP-4) inhibitors [143–147], can work well, with or without basal insulin [148–150]. The risk of hypoglycaemia is low while managing mild to moderately raised glucose concentrations. The use of sitagliptin was also beneficial in a retrospective cohort study looking at people admitted with SARS-CoV-2 infection, where the addition of this drug at the time of admission was associated with a lower mortality compared to standard of care [151]. SGLT-2 inhibitor use in the outpatient setting has been associated with cardiovascular benefit, in particular with respect to heart failure and the progression of diabetes-related renal disease [118–123]. Use in the acute hospitalization setting remains controversial, because of the potential risk of dehydration, worsening renal function, and DKA. A small study looking at the use of empagliflozin in acute heart failure showed no change in dyspnoea, diuretic response, or NT-proBNP concentration [124]. However, it did show a reduction in urine output, leading to less heart failure and lower 60-day mortality rates [124]. A recent study looking at the use of dapagliflozin in people with and without diabetes admitted with Covid-19 infection and at least one cardiovascular risk factor showed no differences in outcomes compared to those given placebo [152]. These authors showed that the use of dapagliflozin was not associated with significant side effects, with only 2 people out of the 312 in the group given the drug who had diabetes developing 'mild' DKA, which resolved on withdrawal of the drug [152]. Because of the lack of robust evidence of benefit, routine use of SGLT-2 inhibitors in hospital is not recommended outside of a clinical trial setting [125].

With respect to insulin, Umpierrez et al. used more flexible insulin regimens, either with or without non-sulfonylurea oral agents, with some success in medical and surgical patients [153, 154]. Subcutaneous insulin given as a basal bolus regimen with correction bolus doses has also been used [154]. However, these regimens require a degree of awareness and training among nursing and medical staff. Insulin administration errors are common and have been classified as a *never event* [155]. When incidents occur, they should be reviewed as part of a route cause analysis, regularly audited, and staff training put into place as necessary.

Technology

The use of technology to manage diabetes in hospital has evolved rapidly over the last few years, but remains some way from routine clinical use [156–159]. Trials of continuous glucose monitoring [160, 161] and the use of closed-loop systems have been conducted. Continuous subcutaneous insulin infusion use is not advocated in those who are unwell or unable to use the equipment [162]. Continuous subcutaneous insulin infusions complemented by implantable real-time glucose sensors have been used successfully in small studies [163–166]. They reduce the time spent in hypoglycaemia and also increase the time in range. The use of this technology is likely to become more frequent as the algorithms become more sophisticated, the risks of dysglycaemia lessen, and the cost of the technology falls sufficiently to make it cost-effective to use regularly [156].

Subcutaneous and intravenous insulin protocols

The ideal intravenous or subcutaneous insulin protocol should be safe, understandable, easily ordered, and readily implemented. It should be effective in correcting hyperglycaemia quickly and in maintaining glucose levels within a defined target range. If insulin is given intravenously, the provision of an easy-to-follow algorithm for making incremental changes to the infusion rate, which can be executed by nursing staff, is likely to improve the efficacy of the protocol.

The terms *variable-rate intravenous insulin infusion* (VRIII) and *fixed-rate intravenous insulin infusion* (FRIII) are preferred owing to the potential ambiguity associated with the term *sliding scale*. VRIII should only be used in situations where the person with diabetes is very sick, during labour and delivery, or when the person is unable to eat or drink normally. Whether the individual has previously recognized diabetes or not, insulin provides the greatest flexibility to meet rapidly changing requirements in different hospital settings to achieve optimal blood glucose levels. The indications for an intravenous insulin infusion are shown in Box 39.1 [167].

Box 39.1 Indications for an Intravenous Insulin Infusion

Hyperglycaemia in:
- Those with known diabetes or with hospital-related hyperglycaemia unable to take oral fluid/food and for whom adjustment of their own insulin regime is not possible.
- Vomiting (exclude diabetic ketoacidosis).
- Nil by mouth and will miss more than one meal.
- Severe illness with need to achieve optimal glycaemic levels, e.g. sepsis.

Special circumstances:
- Acute coronary syndrome (follow local guidelines).
- Total parenteral nutrition/enteral feeding.
- Steroid use.
- Pregnancy.

Source: Modified from George et al. 2015 [167].

Table 39.1 An example of an intravenous insulin infusion regimen.

Glucose (mmol/l)	Insulin rates (ml/h)[a] (start on standard rate unless otherwise indicated)[b]		
	Reduced rate (for use in insulin-sensitive individuals, e.g. ≤24 units/day)	Standard rate (first choice in most individuals)	Increased rate (for insulin-resistant individuals, e.g. ≥100 units/day)
<4.0	0	0	0
4.1–8.0	0.5	1	2
8.1–12.0	1	2	4
12.1–16.0	2	4	6
16.1–20.0	3	5	7
20.1–24.0	4	6	8
>24.1	6	8	10

[a] Using 50 units of human soluble insulin in 49.5 ml of 0.9% sodium chloride solution gives a concentration of 1 unit/ml.
[b] If the individual normally takes basal subcutaneous insulin, continue this alongside the variable-rate intravenous insulin infusion.
The scales may be customized as necessary.
Source: Modified from George et al. 2015 [167].

FRIII should only be used when treating hyperglycaemic crises, DKA, or hyperosmolar hyperglycaemic syndrome (HHS) [24, 48]. The use of insulin regimens where the dose administered is dependent on the capillary glucose concentration with the insulin given intravenously or subcutaneously as the only means of managing a raised glucose concentration has been soundly discredited, but disappointingly continues [167–170]. Basal bolus regimens of subcutaneous insulin have been used successfully to manage glucose levels on medical and surgical wards [11, 154, 172].

How insulin is given is also a subject of contention. There is evidence for the use of a *basal plus* regimen, where a single daily dose of basal insulin is given along with six-hourly corrective doses of rapid-acting insulin if the person is not eating or drinking, or if glucose concentrations are high before meals [173, 174]. Twice-daily mixed subcutaneous insulin regimens have previously been advocated [3, 175], but their use is associated with high rates of iatrogenic hypoglycaemia, especially in the context of variable oral intake [176].

To use insulin safely requires a certain level of understanding, which is lacking among many junior medical staff, students, and nurses [72–74]. This may be why there is reluctance among junior medical staff to prescribe subcutaneous insulin earlier, even when glucose concentrations remain high.

Hypoglycaemia is a potential complication of intensified insulin therapy and is associated with poor outcomes. Thus intravenous insulin infusions should be supported by caloric input when glucose concentrations drop. In most people, this is in the form of a simultaneous infusion of glucose-containing fluid, but calories can be provided by other routes (e.g. enteral, parenteral, or in dialysis fluid). If the patient was taking a long-acting basal insulin (human or analogue) prior to admission, then this should be continued, because continuation of the background insulin prevents rebound hyperglycaemia or development of ketosis when the intravenous insulin is stopped [177].

Preparation and delivery of an intravenous insulin infusion

An intravenous insulin infusion is prepared by adding 50 units of soluble insulin to 49.5 ml of 0.9% sodium chloride solution, providing 1 unit of insulin in 1 ml, which is delivered via an infusion pump. This insulin infusion can be piggy-backed into the glucose infusion using a three-way connector and a non-return valve. This is most often given as a variable-rate intravenous insulin infusion; it can be given as an FRIII, but this is limited to treatment of DKA or HHS (Table 39.1).

Transition from intravenous to subcutaneous insulin

Conversion to subcutaneous insulin should only be undertaken when the individual is able to eat and drink normally without nausea or vomiting. The most appropriate time to switch from intravenous to subcutaneous insulin is at the usual time of the person's subcutaneous insulin administration before a meal; however, when possible, this should not be done before the evening meal. People with type 1 diabetes will become insulin deficient within minutes of an intravenous infusion being stopped because of the short half-life of intravenous insulin. It is therefore good practice to continue the infusion of insulin for approximately 60 minutes after the subcutaneous insulin has been administered to allow time for the insulin to be absorbed [167].

If the person with diabetes has been on an established insulin regimen that has worked well, then this regimen should be restarted, but doses may have to be adjusted depending on the clinical condition. If the individual is new to insulin therapy, or if the previous regimen provided inadequate glycaemic levels (e.g. as evidenced by a raised HbA_{1c}), then a rough estimation of the total daily dose (TDD) of insulin required can be made from a simple calculation using the hourly rates delivered in the intravenous insulin infusion. Estimation of insulin doses can also be made according to body weight, which is useful in calculating TDD requirement in individuals who are new to insulin but have not required an insulin infusion (Table 39.2 and Box 39.2).

Avoiding and treating in-hospital hypoglycaemia

Hypoglycaemia, the commonest side effect of insulin and sulfonylurea treatment, represents a major barrier to satisfactory long-term glycaemic management. The other drug classes – that is, biguanides,

Table 39.2 Transition from intravenous to subcutaneous insulin.

Insulin	Optimal glucose levels, i.e. HbA_{1c} <59 mmol/mol (7.5%)	Suboptimal glucose levels	Monitoring blood glucose for all individuals
Basal insulin	Restart usual dose of insulin when it is due (usually with either breakfast or evening meal). Do not stop VRIII until at least 30–60 min after insulin has been given and patient has eaten If it is necessary to stop VRIII but the basal insulin is not due for several hours, give half the usual dose of basal insulin. This will provide background insulin until the usual dose can be recommenced	In addition, discuss with local diabetes inpatient team. Insulin regimen may need adjusting	CBG should be checked 1 h after discontinuing VRIII and at least 4-hourly for the next 24 h, to ensure that there is no rebound hyper- or hypoglycaemia
Once- or twice-daily mixed insulin	Restart usual dose of insulin together with a meal (either breakfast or evening meal). Do not stop VRIII until at least 30–60 min after insulin has been given and the individual has eaten If it is necessary to stop VRIII at lunchtime, give half the usual breakfast dose of mixed insulin. This will provide essential background insulin until the usual dose can be recommenced		
Multiple daily insulin injections (MDI or basal bolus)	Restart usual diabetes treatment together with a meal Basal insulin will usually have been continued. Restart bolus dose of insulin together with the next meal. Do not stop VRIII until at least 30–60 min after bolus insulin has been given and the individual has eaten If basal insulin has been stopped, background insulin must be restarted prior to stopping VRIII. Ideally, continue VRIII until basal insulin is given and a meal is due, and stop at least 30–60 min after basal and bolus insulin is restarted If it is necessary to stop VRIII, but basal insulin is not due for several hours, give half the usual daily dose of basal insulin, along with a meal and bolus insulin. This will provide essential background insulin until the usual dose can be recommenced		
Insulin pump (CSII)	Restart usual basal rate via CSII Do not stop VRIII until at least 30 min after insulin has been recommenced via CSII Give bolus insulin according to patient's usual regime. It is not typically necessary to wait until a mealtime to switch back to CSII therapy Avoid restarting CSII at bedtime		

CBG, capillary blood glucose; CSII, continuous subcutaneous insulin infusion; HbA_{1c}, glycated haemoglobin; VRIII, variable-rate intravenous insulin infusion.
Source: Modified from George et al. 2015 [167].

Box 39.2 Converting from Intravenous to Subcutaneous Insulin

Step 1
Calculate the total daily dose (TDD) using either of two methods: weight based, or using the dose delivered for the last six hours using a variable-rate intravenous insulin infusion (VRIII).
In frail, older individuals, those with renal failure (chronic kidney disease stage 4 or 5) or severe hepatic failure, or those with newly diagnosed type 1 diabetes:

TDD = 0.3 × body weight in kg

All other adults:

TDD = 0.5 × body weight in kg

Ideally, 24 hours of data should be utilized to make the calculation, but if this is not available then all available data on hourly insulin requirements should be used. For example, if six hours of data are available, then the calculation is as follows:

Total dose of insulin administered in the last 6 hours of the VRIII / 6 = average hourly dose Average hourly dose × 20 (not 24, to reduce risk of hypoglycaemia) = estimated TDD

Step 2
Use the TDD to convert the individual to either a premixed twice-daily insulin regimen or a multiple basal bolus dose regimen.

For a basal bolus regimen, 50% of the TDD is usually given as basal insulin, and the remainder as rapid-acting insulin, divided equally between breakfast, lunch, and evening meal.

For a twice-daily, premixed insulin regimen, individuals usually need 60% of the TDD at breakfast and the remaining 40% with the evening meal.

Source: Modified from George et al. 2015 [167].

thiazolidinediones, DPP-4 inhibitors, SGLT-2 inhibitors, and glucagon-like peptide 1 (GLP-1) receptor agonists – are unlikely to result in hypoglycaemia owing to their modes of action, unless co-prescribed with insulin or sulfonylureas. Hypoglycaemia should be excluded in any person with diabetes who is acutely unwell, drowsy, unconscious, unable to cooperate, or presenting with aggressive behaviour or seizures. In-hospital hypoglycaemia is defined as a blood glucose level ≤3.9 mmol/l (70 mg/dl) [81]. Hypoglycaemia in hospital is widespread and coupled with insufficient knowledge of how to detect and manage it [82, 142].

Frequency of hypoglycaemia in hospital

Hypoglycaemia is given as the primary cause of hospital admission in about 5% of all people admitted with type 1 diabetes, and 1.5% of those with type 2 diabetes [178]. The 2019 UK NaDIA showed that 16.5% of people with diabetes in hospital experienced one or more hypoglycaemic episodes with a blood glucose less than 3.0–4.0 mmol/l (54–72 mg/dl), with 6.8% experiencing one or more hypoglycaemic episodes below than 3.0 mmol/l (54 mg/dl), and 1.4% requiring rescue treatment with intravenous glucose or intramuscular glucagon [4].

Farrokhi et al. reported a prevalence of severe hypoglycaemia ranging from 5% to 32% in those treated with insulin [179]. The highest proportion of episodes took place overnight (34.3%), between 9 p.m. and 9 a.m., when snack availability was likely to have been lowest; these observations have been confirmed elsewhere [180]. People treated with sulfonylureas were more likely to experience hypoglycaemia than those using insulin (75.3% vs 59.3%) [103, 180, 181].

The tight glycaemic levels achieved in ICUs led to much higher reported rates of hypoglycaemia, with the incidence of blood glucose ≤2.2 mmol/l (40 mg/dl) ranging from 5% to 18.7% [83, 87, 89, 182].

Causes of in-hospital hypoglycaemia

Common causes of hypoglycaemia are listed in Table 39.3. One of the most serious and common causes of hypoglycaemia is insulin prescription errors, including misreading poorly written prescriptions, such as when U is used for units (e.g. 4 U becoming 40 units), or confusing the insulin name with the dose (e.g. Humalog Mix25 becoming Humalog 25 units). The advent of electronic prescribing may be responsible for the small reductions in prescribing errors reported by NaDIA [103]. Risk factors for hypoglycaemia include older age (>70 years), cognitive impairment, nephropathy, insulin or sulfonylurea treatment, being of Black, Asian or minority ethnic groups, raised C-reactive protein, being admitted as an emergency, and having low sodium or albumin concentrations [181, 184, 185].

Mortality and length of stay associated with in-hospital hypoglycaemia

Lake et al. published a systematic review and meta-analysis on the effects of hypoglycaemia during a hospital admission [112]. They found that experiencing a blood glucose of <4.0 mmol/l (72 mg/dl) led to an increased length of stay of 4.1 days (95% confidence interval [CI] 2.36 to 5.79) compared to those who did not. In addition, the relative risk (RR) of mortality was double (RR 2.09; 95% CI 1.64 to 2.67) [112]. Those experiencing an episode of hypoglycaemia had a 66% increased risk of death within one year, compared to those with no hypoglycaemia [186].

Management of in-hospital hypoglycaemia

People experiencing hypoglycaemia require prompt treatment with quick-acting carbohydrate to return their blood glucose levels to the normal range. The quick-acting carbohydrate should be followed by giving long-acting carbohydrate, either as a snack or as part of a planned meal. When it is safe to do so, a blood glucose measurement should be taken to confirm hypoglycaemia (especially if there is any suspicion that the person may be currently under the influence of alcohol or non-prescription drugs). If measurement is difficult (e.g. during a seizure), then treatment should not be delayed.

Adults who have suboptimal glycaemic levels may start to experience symptoms of hypoglycaemia at blood glucose levels >4.0 mmol/l (72 mg/dl), but the thresholds for cognitive dysfunction are unaffected; therefore, the only reason for treatment is symptomatic relief. Hence adults who are experiencing hypoglycaemia symptoms but have a blood glucose level >4.0 mmol/l (72 mg/dl) should be treated with a small carbohydrate snack only, such as a medium banana, a slice of bread, or a normal meal if due. All adults with a blood glucose level <4.0 mmol/l (72 mg/dl) with or without symptoms of hypoglycaemia should be treated as shown in Figure 39.2.

When rescue treatment is required, intramuscular glucagon should only be given once. It should not be given to those with a

Table 39.3 Potential causes of in-hospital hypoglycaemia.

Medical issues	Carbohydrate intake issues
• Inappropriate use of stat or PRN rapid/short-acting insulin • Acute discontinuation of long-term steroid therapy • Recovery from acute illness/stress • Mobilization after illness • Major amputation of a limb • Incorrect type of insulin or oral hypoglycaemic therapy prescribed and administered • Inappropriately timed insulin or oral hypoglycaemic therapy in relation to meal or enteral feed • Change of insulin injection site • Intravenous insulin infusion with or without glucose infusion • Inadequate mixing of intermediate-acting or mixed insulins • Regular insulin doses or oral hypoglycaemia therapy being given in hospital when these are not routinely taken at home	• Missed or delayed meals • Less carbohydrate than normal • Change of timing of the biggest meal of the day (i.e. main meal at midday rather than evening) • Lack of access to usual between-meal or before-bed snacks • Prolonged starvation time, e.g. nil by mouth • Vomiting • Reduced appetite • Reduced carbohydrate intake

PRN, as required.
Source: Modified from Stanisstreet et al. 2020 [183].

Figure 39.2 Algorithm for the treatment of hypoglycaemia in adults with diabetes in hospital. Hypoglycaemia is defined as a blood glucose level of <4.0 mmol/l (72 mg/dl). If the patient is symptomatic but the blood glucose is >4.0 mmol/l (72 mg/dl), then a small carbohydrate snack should be given for symptom relief. ABC, airway, breathing, circulation; CDE, certified diabetes educator; DSN, diabetes specialist nurse; NBM, nil by mouth. Source: Joint British Diabetes Societies for Inpatient Care 2022 [183].

history of known liver disease, or those with depleted glycogen reserves (e.g. alcohol excess), because it will likely be considerably less effective. A new formulation of intranasal glucagon has recently become available that has a similar efficacy to the intramuscular formulation [187]. When intravenous glucose is required 10% glucose is preferred, because retreatment rates were the same as those for 50% glucose, with lower risk of extravasation injury and lower likelihood of resultant high blood glucose concentrations [183, 188].

Evidence for treatment options

There is limited evidence regarding the quantity of quick-acting carbohydrate required to treat an episode of hypoglycaemia successfully. The initial quantities chosen were the result of expert consensus subsequently backed up by glucose clamp studies [189, 190]. Subsequent work has shown that ~20 g of rapid-acting carbohydrate is often sufficient, with less than 10 g likely to be inadequate [191, 192]. Chocolate- and sucrose-containing foods should be avoided, because the high fat content in chocolate slows gastric emptying, thus delaying absorption, and sucrose needs to be cleaved by intestinal disaccharidases prior to absorption [193, 194]. Fresh fruit juice or glucose-containing tablets or gel remain the most frequently used treatment for hypoglycaemia and are an essential component of Hypoboxes, which are commercially available [183, 190, 195]. The suggested contents of a Hypobox can be found in Box 39.3.

All hypoglycaemic events should be documented in the clinical records. The underlying cause of hypoglycaemia should be investigated and risk of recurrence reduced where possible. Regular capillary blood glucose monitoring should be continued for 24–48 hours. The person with diabetes should be told to continue this at home if they are to be discharged. Hypoglycaemia education should be given or a referral made to the DISN/CDE.

Box 39.3 Suggested Contents of a Hypobox

- A copy of the locally agreed hypoglycaemia algorithm (laminated and attached to the inside of the lid)
- 2 × 200 ml cartons of fruit juice
- 2 packets of glucose tablets
- 1 mini-pack of biscuits (source of long-acting carbohydrate)
- 3 tubes (one box) of glucose gel
- 20% glucose intravenous solution (100 ml vial)
- 1 × 18G intravenous cannula
- 1 × 16G intravenous cannula
- 1 × 10 ml sterile syringe
- 3 × 10 ml 0.9% sodium chloride solution ampoules for flush
- 1 × 21G sterile needle
- Chlorhexidine spray/alcohol wipes
- 1 dressing cover for the intravenous cannula
- 10% glucose for intravenous infusion (500 ml bag)
- Audit form
- Instructions on where to send the audit form and replenish supplies
- 1 glucagon pack: to be kept in the nearest drug refrigerator or labelled with a reduced expiry date of 18 months if it is stored at room temperature

Source: Modified from JBDS 2020 [183].

Surgery in people with diabetes

Perioperative and postoperative hyperglycaemia is associated with short- and long-term harm, which has been reported in many settings, including general surgery [53, 54], cardiac surgery [196], vascular surgery [197, 198], neurosurgery [199], orthopaedic surgery [200, 201], colorectal surgery [202], trauma [203], breast surgery [204], liver transplantation [205], hepatobiliary and pancreatic surgery [206], cholecystectomy [207], burns [58], and foot and ankle surgery [208]. These harms include surgical site infection [59], length of time in hospital, acute kidney injury, myocardial infarction, time spent in an ICU or on a ventilator, and death. The perioperative mortality rate is up to 50% higher than in people without diabetes [54]. In addition, people with diabetes are less likely to be offered day-case surgery, are more likely to have emergency surgery, have longer lengths of stay following admission, and have a higher rate of 28-day readmission following surgery [209]. Thus, there is an imperative to optimize glycaemic levels prior to surgery and around the time of the operation. However, for elective surgery this optimization would require a great deal of coordination between all the teams and individuals involved in the care of the person with diabetes. In the UK, the National Confidential Enquiry into Patient Outcome and Death conducted a study into perioperative care and showed that there were several parts of the patient journey that could be improved [61]. Its recommendations are listed in Table 39.4.

Currently, there is a lack of good communication between primary care and surgeons when referring for elective surgery [60, 61]. This is important, because individuals who have been identified as having diabetes prior to surgery have a significantly lower risk of poor outcomes, regardless of their glycaemic levels [53]. This may be because of the improved communication between staff. Furthermore, if an individual is treated with an intravenous insulin infusion, it is likely that they will have more frequent contact with nursing staff, if only to have a capillary glucose measurement taken. Indeed, pooled data from a large number of Veterans Affairs (VA) hospitals in the USA suggested that people known to have diabetes were more likely to have their glucose checked postoperatively (with higher preoperative HbA_{1c} being associated with a higher number of tests) [75]. In addition, those with higher postoperative glucose concentrations were more likely to go onto insulin [75]. Hence if complications do occur, they may be picked up at an earlier stage.

In the UK, the JBDS guideline for the perioperative management of adults with diabetes recommends that the glucose targets for patients undergoing surgery are to keep levels between 6.0 and 10.0 mmol/l (108 and 180 mg/dl), with an acceptable range of 4.0–12.0 mmol/l (72–216 mg/dl) in the awake surgical patient [55]. In those who are asleep, or unable to communicate, the risk of developing hypoglycaemia increases at the lower limit, hence the range is recommended to be 6.0–12.0 mmol/l (108–216 mg/dl) [86, 210]. The USA and other countries do not yet have similar guidelines, although given the recent evidence that a perioperative HbA_{1c} level of >8.0% (64 mmol/mol) is associated with greater harm, organizations may begin to address this in the future [140, 211].

Due to the greatly increased risk of postoperative complications associated with hyperglycaemia, it may be necessary for units to adopt a policy to measure a capillary glucose level in at-risk individuals at the preoperative assessment clinic or at the time of acute admission, to ensure that those with undiagnosed hyperglycaemia,

Table 39.4 List of recommendations around peri-operative diabetes care made by the UK National Confidential Enquiry into Patient Outcome and Death in its report on perioperative diabetes care.

1. Write and implement a national joint standard and policy for the multidisciplinary management of patients with diabetes who require surgery.
2. Appoint a clinical lead for perioperative diabetes care in hospitals where surgical services are provided.
3. Use a standardized referral process for elective surgery to ensure appropriate assessment and optimization of diabetes.
4. Ensure that patients with diabetes undergoing surgery are closely monitored and their glucose levels managed accordingly.
5. Ensure a safe handover of patients with diabetes from theatre recovery to ward, which should be documented in the case notes.
6. Develop a preoperative assessment clinic policy and standards for the management of patients with diabetes. These should be developed by the lead anaesthetist and the clinical lead for perioperative diabetes management.
7. Ensure that patients with diabetes attending a preoperative assessment clinic prior to elective surgery have (i) access to the diabetes multidisciplinary team; and (ii) written instructions regarding their diabetes management plan prior to surgery.
8. A clinical lead for day surgery should be in place in all hospitals providing day surgery services.
9. Cancellation of elective surgery in patients with diabetes should be avoided, particularly for known clinical reasons.
10. Develop and implement referral criteria for surgical inpatients with diabetes to members of the diabetes multidisciplinary team members as required.
11. Record and monitor the time at which a patient begins fasting (for surgery or clinical reasons).
12. Prioritize patients with diabetes on the operating list to avoid prolonged starvation.
13. Provide patients with diabetes with education and information about their diabetes management at discharge from hospital as part of the discharge planning process.

Source: Modified from National Confidential Enquiry into Patient Outcome and Death 2018 [61].

either diabetes or stress hyperglycaemia, can be identified early and appropriately treated promptly.

Potential mechanisms of beneficial effects of glucose lowering in surgical settings

Although the data to show that lowering blood glucose is beneficial in surgical patients are only emerging now, it is well recognized that insulin has several beneficial effects on the inflammatory cascade that are independent of its metabolism-regulating effect. These effects include reducing the degree of oxidative stress by its action on free radical production and clearance [213], and also beneficial effects on reducing pro-inflammatory cytokine levels in addition to improving white cell and endothelial function [213–215]. These effects may be in part responsible for the reduction in surgical site infections and reduced mortality seen when optimal glucose concentrations are maintained [78,216]. What constitutes *optimal glycaemic management*, however, varies between studies [216].

The role of primary care in supporting diabetes care before elective surgery

The patient journey for elective surgery usually starts with a primary care assessment and referral to the surgeons [55]. A study of 1919 referrals made to all surgical specialties across 11 hospitals across one week in the East of England showed that communication between primary and secondary care at the time of referral for a surgical opinion is poor [60]. There were 8.8% of referrals for people with diabetes (compared to the 6.5% prevalence of diabetes in the general population). Of those taking a glucose-lowering agent, 22% had diabetes mentioned as a comorbidity in the letter. Only 7.7% of those with diabetes had a recent HbA_{1c} documented, and 11.8% had the medication listed [60]. While a meta-analysis suggested that there was no relationship between HbA_{1c} and outcomes in surgical patients [217], studies have shown that improving glycaemic management reduces the risk of developing surgical site infections [78].

In the absence of randomized controlled trials, the current guidelines are pragmatic because it is well recognized that high-risk surgical patients are often older and have multiple coexisting medical conditions. Attempts to lower glycaemic levels aggressively may be associated with harm in the form of hypoglycaemia. However, HbA_{1c} levels >64 mmol/mol (8%) are associated with poor outcomes [211] and the UK National Guidelines suggest that HbA_{1c} should be <69 mmol/mol (8.5%) [55]. Hence it is incumbent on the primary care provider to optimise glycaemic levels prior to referral, if possible, or after referral is made, to reduce the risk of the procedure being cancelled or postponed owing to hyperglycaemia and the risk of harm postoperatively. The information provided by the primary care team should help the surgeon when individuals are seen in the surgical outpatient clinic.

Preoperative assessment

If the decision is made to operate, then the surgeon should communicate the presence of diabetes to the preoperative assessment team, the anaesthetists, and the operating list planners, so that the patient may be placed early on a theatre list to minimize starvation time and subsequent metabolic disturbance. This would also increase the likelihood that they could be same-day admissions. In addition, the provision should be made for postoperative admission to critical care, if this is indicated, especially with people who are at high risk and with suboptimal glycaemic levels.

The opportunity to optimize preoperative glycaemic levels should be taken, either by referring back to the primary healthcare team responsible for their diabetes or using a DSN or CDE as necessary [209]. The management of other comorbidities should also be optimized. There should be good lines of communication between the pre-assessment team and the surgical team, such that the patient is aware when they are due to come in, where they are due to go, and what time their surgery is. They should also have explicit written instructions on how to manage their diabetes medication. These are shown in Tables 39.5 and 39.6.

Many people with diabetes in the UK have been inappropriately denied day-case surgery [6]. This means that these individuals are unnecessarily admitted to hospital for an overnight hospital stay, adding to the cost burden, in the belief that being in hospital will lead to glycaemic optimization. However, the reality is likely to be that the person is admitted to a ward the evening prior to surgery, when there are fewer nursing staff available, treated with a VRIII, and looked after by one of the most junior members of the medical team, who may have inadequate levels of knowledge of diabetes management [72–74]. More recently, initiatives have been put into place in many institutions to improve perioperative care [218, 219].

Hospital admission

During the hospital admission, it is important that the individualized care plan is communicated to all staff involved in the care of the person with diabetes and that all efforts are made to minimize the metabolic consequences of starvation and surgical stress. Work

Table 39.5 Guidelines for perioperative adjustment of insulin.

	Insulins	Day prior to admission	Morning surgery	Afternoon surgery
Long-acting insulin	Once-daily long-acting (morning) (e.g. Hypurin®, Bovine Lente, Lantus®, Levemir®, Tresiba®, Insulatard®, Humulin I®, Insuman Basal®, Abasaglar®, Toujeo®, Semglee®, Xultophy®)	Doses should remain unchanged	Dose will need to be reduced by 20% and blood glucose should be checked on admission	Dose will need to be reduced by 20% and blood glucose should be checked on admission
	Once-daily long-acting (lunchtime) (e.g. Hypurin®, Bovine Lente, Lantus®, Levemir®, Tresiba®, Insulatard®, Humulin I®, Insuman Basal®, Abasaglar®, Toujeo®, Semglee®, Xultophy®)	Dose will need to be reduced by 20%	Restart insulin at normal dose when eating and drinking	Restart insulin at normal dose when eating and drinking
	Once-daily long-acting (evening) (e.g. Hypurin®, Bovine Lente, Lantus®, Levemir®, Tresiba®, Insulatard®, Humulin I®, Insuman Basal®, Abasaglar®, Toujeo®, Semglee®, Xultophy®)	Dose will need to be reduced by 20%	No dose adjustment necessary	No dose adjustment necessary
	Twice-daily long-acting (e.g. Hypurin®, Bovine Lente, Lantus®, Levemir®, Tresiba®, Insulatard®, Humulin I®, Insuman Basal®, Abasaglar®, Toujeo®, Semglee®, Xultophy®)	Morning dose will need to stay the same Evening dose will need to be reduced by 20%	Morning dose will need to be reduced by 20% and blood glucose should be checked on admission	Morning dose will need to be reduced by 20% and blood glucose should be checked on admission
			Evening dose will remain unchanged	Evening dose will remain unchanged
Premixed insulin	Twice-daily premixed (e.g. Novomix 30®, Humulin M3®, Humalog Mix 25®, Humalog Mix 50®, Insuman Comb 15®, Insuman Comb 25®, Insuman Comb 50®, Hypurin Porcine 30/70 Mix®)	Morning and evening doses should remain unchanged	Halve usual morning dose. Blood glucose should be checked on admission	Halve usual morning dose. Blood glucose should be checked on admission
			Resume normal insulin with evening meal	Resume normal insulin with evening meal
	Three times per day premixed (e.g. Novomix 30®, Humulin M3®, Humalog Mix 25®, Humalog Mix 50®, Insuman Comb 15®, Insuman Comb 25®, Insuman Comb 50®, Hypurin Porcine 30/70 Mix®)	Doses should remain unchanged	Halve usual morning dose. Blood glucose will be checked on admission	Halve usual morning dose. Blood glucose should be checked on admission
			Omit lunchtime dose	Omit lunchtime dose
			Resume normal insulin with evening meal	Resume normal insulin with evening meal
Mixture of short- and intermediate-acting insulin	Twice-daily (two different types of insulin) combined by the patient into one injection Short-acting (e.g. Insuman Rapid®, Humalog®, Actrapid®, Hypurin® Bovine Neutral, Hypurin® Porcine Neutral, NovoRapid®, Humulin S®, Apidra®, Fiasp®, Lyumjev®) AND intermediate-acting (e.g. Hypurin® Bovine Isophane, Hypurin® Porcine Isophane, Insulatard®, Humulin I®, Insuman Basal®)	Morning and evening doses should remain unchanged	Calculate the total dose of both morning insulins and give half of this total dose as intermediate-acting insulin only, in the morning	Calculate the total dose of both morning insulins and give half of this total dose as intermediate-acting insulin only, in the morning
			Blood glucose should be checked on admission	Blood glucose should be checked on admission
			Resume normal insulin with evening meal	Resume normal insulin with evening meal
Short-acting insulin	Short-acting insulin with meals (2–4 doses a day) (e.g. Insuman Rapid®, Humalog®, Actrapid®, Hypurin® Bovine Neutral, Hypurin® Porcine Neutral, NovoRapid®, Humulin S®, Apidra®, Fiasp®, Lyumjev®)	Doses should remain unchanged	Omit morning dose if no breakfast is eaten	Take usual morning insulin dose with breakfast
			Blood glucose should be checked on admission	Omit lunchtime dose if not eating
			Omit lunchtime dose if not eating and drinking normally	Blood glucose should be checked on admission
			Resume normal insulin with evening meal	Resume normal insulin with evening meal

Resume taking normal insulin the morning after surgery (procedure). However, blood glucose may be higher than usual for a day or so.

If a variable-rate intravenous insulin infusion is used, then the dose of long-acting insulin should be reduced by 20%. Short-acting, intermediate, and pre-mixed insulins should be discontinued. Normal insulin doses should be recommenced when that person is eating and drinking normally.

At the preoperative assessment clinic, all individuals should have emergency treatment for hypoglycaemia written on their drug chart, i.e. 40% glucose gel, and 20% glucose rapid-acting insulin should also be prescribed.

If the patient requires an ongoing variable-rate intravenous insulin infusion, then the long-acting background insulin should be continued but at 80% of the usual dose. Normal insulin doses should be recommenced when the person is eating and drinking normally.

Source: Modified from Dhatariya et al. 2015 [55].

Table 39.6 Guidelines for perioperative adjustment of non-insulin medication.

Diabetes medication	Day prior to admission	Timing of surgery		
		Morning. surgery	Afternoon surgery	If a VRIII is being used
Acarbose	Take as normal	Omit morning dose if *not* eating	Give morning dose if eating	Stop if VRIII running, do not restart until eating and drinking normally
Meglitinide (repaglinide or nateglinide)	Take as normal	Omit morning dose if *not* eating	Give morning dose if eating	VRIII running, do not restart until eating and drinking normally
Metformin (eGFR >60 ml/min/1.73 m^2 and procedure not requiring use of contrast media, or major liver surgery[a])	Take as normal	If taken once or twice a day – take as normal If taken three times per day, omit lunchtime dose	If taken once or twice a day – take as normal If taken three times per day, do not take lunchtime dose	VRIII running, do not restart until eating and drinking normally
Sulfonylurea (e.g. glibenclamide, gliclazide, glipizide, glimepiride)	Take as normal	Omit on morning of surgery If taken twice daily, take evening dose	Do not take on day of surgery	VRIII running, do not restart until eating and drinking normally
Pioglitazone	Take as normal	Take as normal	Take as normal	VRIII running, do not restart until eating and drinking normally
DPP-4 inhibitor (e.g. sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin)	Take as normal	Take as normal	Take as normal	VRIII running, do not restart until eating and drinking normally
GLP-1 receptor agonist (e.g. exenatide, liraglutide, lixisenatide, dulaglutide, semaglutide)	Take as normal	Take as normal	Take as normal	Take as normal
SGLT-2 inhibitor[b] (e.g. dapagliflozin, canagliflozin, empagliflozin, ertugliflozin) Sotagliflozin (an SGLT-1/2 inhibitor)	Take as normal	Do not take on day of surgery	Do not take on day of surgery	Omit until eating and drinking normally
The person with diabetes should resume taking their normal tablets the morning after surgery if they are eating and drinking normally. Warn the person with diabetes that their blood glucose control may be erratic for a few days after the procedure. In the case of major liver surgery (i.e. removal of three or more liver segments), then metformin should be stopped 48 h prior to surgery.				

DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1; NBM, nil by mouth; SGLT-2, sodium–glucose co transporter 2; VRIII, variable-rate intravenous insulin infusion.

[a] If contrast medium is to be used and eGFR <60 ml/min/1.73 m^2, metformin should be omitted on the day of the procedure and for the following 48 h.

[b] If there is likely to be a period of reduction in oral intake prior to a procedure – e.g. colonoscopy – then the drug should be omitted starting on the day of the reduced intake. This may mean omitting the drug the day prior to the procedure, as well as the day of the procedure. US and other guidelines recommend stopping SGLT2 inhibitors 72 hours prior to a planned procedure.

Source: Modified from Dhatariya et al. 2015 [55].

has shown that adequate staff education can be difficult to achieve [220–222]. At the same time, optimal glycaemic levels should be achieved using the standard of care for that institution, such as a basal bolus insulin regimen [154, 173]. The principles of the enhanced recovery after surgery programme should be put into place. However, the role of preoperative carbohydrate loading in people with diabetes remains controversial [223]. When the starvation time is short – that is, less than one missed meal – there is no need for a VRIII; however, if the starvation period is likely to be longer, then one should be *in situ* and the use of long-acting insulin should be continued to prevent rebound hyperglycaemia when the intravenous insulin regimen is stopped [177]. During the entire admission, pressure areas, including heels and feet, should be regularly inspected.

In the operating theatre and recovery

While the person with diabetes is in theatre and in recovery, glucose and electrolyte concentrations should be monitored and normoglycaemia should be maintained [225]. The use of multimodal analgesia with an appropriate antiemetic to permit an early return to a normal diet and the usual diabetes regimen is paramount, although the use of dexamethasone in this situation remains a matter for debate [225].

Postoperative period

Several factors influence glycaemic levels in the postoperative period, including a variation in nutritional intake, the discontinuation of the usual blood glucose-lowering medication, the decrease in physical activity, the increase in stress hormones, and the presence of infection or pain. It is therefore important that glycaemic levels are maintained in addition to fluid and electrolyte balance and that pain and postoperative nausea and vomiting are controlled.

Hospital discharge

In the preoperative stage and prior to hospital discharge, it is important to identify factors that may delay discharge from hospital and to make the necessary arrangements to allow the person to go back to their usual place of care once medically fit. The person

should be made aware that the metabolic and endocrine effects of surgery may last for several days because of ongoing changes in the amount that they eat, their activity levels, and the levels of stress hormones. The person should be advised that their blood glucose management may need to change for some time postoperatively and that more frequent monitoring may be required. The diabetes specialist team or usual provider of diabetes care should be involved in this discussion.

Emergency surgery

For those requiring emergency surgery where preoperative glycaemic optimization is not possible, the use of a VRIII is likely to be necessary, trying to maintain a blood glucose level between 6.0 and 10.0 mmol/l (108 and 180 mg/dl). This should be continued until the person is eating and drinking normally. Some individuals who are not known to have diabetes may develop transient hyperglycaemia (so-called stress hyperglycaemia) [9, 10]. These individuals should be treated just as aggressively as people known to have diabetes, because their risk of postoperative complications is far higher than in those who were previously known to have diabetes [53, 54, 226].

Continuous subcutaneous insulin infusions (pumps)

The use of an insulin pump depends on the length of surgery and the length of starvation. If the length of starvation is short – that is, less than one missed meal – the pump therapy can usually be continued and the person should remain on their basal rate until they are eating and drinking normally [227]. Regular blood glucose testing is necessary. If, however, the starvation period is likely to be prolonged, then the pump should be discontinued and a VRIII started. If there is a period of post- or perioperative hypotension, or significant use of inotropes, then peripheral skin perfusion may be compromised, thus reducing the absorption of insulin given subcutaneously and possibly necessitating treatment with a VRIII, especially if the person is unable to self-manage. If the insulin pump has been discontinued and replaced with a VRIII, the insulin pump should be restarted once the person is eating and drinking normally and the VRIII should be discontinued 30 minutes after the first mealtime bolus.

There remains some uncertainty about the use of continuous subcutaneous insulin infusion (CSII) during an operation. The use of a diathermy in close proximity to the pump may interfere with its function, so the pump should be placed as far away as possible. Pump manufacturers suggest avoiding pumps when a diathermy is being used, but strategies have been developed to try to use them safely [228, 229].

Glucocorticoid use

Prior to the Covid-19 pandemic and the evidence that glucocorticoid use reduces morbidity and mortality in the infected population [38–42], the prevalence of steroid use in hospitals was estimated to be approximately 13% [36]. The use of steroid treatment in people with pre-existing diabetes is likely to result in worsening glucose levels, which is termed steroid-induced hyperglycaemia. This rise warrants temporary additional, and more active, glycaemic management. A rise in glucose level may occur in people without a known diagnosis of diabetes, and this is termed steroid-induced diabetes. It may or may not resolve when the steroids are withdrawn. Short courses of steroids resulting in minimal periods of hyperglycaemia may not warrant intervention, although higher-dose steroids, for longer periods, may result in significant symptomatic hyperglycaemia with the potential for acute complications [230]. Hence addressing the hyperglycaemia may reduce these risks.

Steroid therapy: impact on blood glucose

Steroids may be administered by various regimens and at variable doses. A single daily dose of steroid (e.g. prednisolone/prednisone) in the morning is the commonest mode of administration. In susceptible individuals, this will often result in a rise in blood glucose by late morning that continues through to the evening. Overnight, the blood glucose generally falls back to baseline levels by the next morning. Therefore, treatment should be tailored to treating the hyperglycaemia, while avoiding nocturnal and early-morning hypoglycaemia.

Multiple daily doses of steroid, be it intravenous hydrocortisone or oral dexamethasone, can cause a hyperglycaemic effect throughout the 24-hour period. A twice-daily premixed or basal bolus regimen may be needed if oral medication or once-daily insulin proves insufficient to treat the hyperglycaemia. Close attention should be paid to blood glucose monitoring and early intervention may be necessary.

Glucose levels in most individuals can be predicted to rise ~4–8 hours following the administration of oral steroids, and sooner following the administration of intravenous steroids. Again, capillary blood glucose monitoring is paramount to guide appropriate therapeutic interventions. Conversely, glucose levels may improve to pre-steroid levels 24 hours after intravenous steroids have been discontinued. If oral steroids are weaned over several weeks, the glucose levels may decline in a dose-dependent fashion, but this may not occur, particularly in those with previously undiagnosed diabetes.

Monitoring

At the commencement of steroid therapy, or for those already on a supraphysiological dose of corticosteroid, capillary blood glucose testing should be initiated twice daily, prior to breakfast and perhaps most appropriately prior to the evening meal, when the hyperglycaemic effect of a morning dose of steroid is likely to be greatest.

Medication options for people taking steroid therapy

Non-insulin therapies

Given their mode of action, a short-acting sulfonylurea taken once daily may best manage the glucose excursion associated with a once-daily oral steroid. The dose of sulfonylurea may be maximally titrated in the morning to reduce the risk of hypoglycaemia. Intuitively, pioglitazone may seem an appropriate choice to manage steroid-induced hyperglycaemia; however, the evidence base for its use is weak [231]. There are currently no data to support the use of GLP-1 receptor agonists or DPP-4 inhibitors; however, their mode of action may suggest that they would be beneficial in this circumstance. A study examining the effect of dapagliflozin in steroid-induced hyperglycaemia showed no benefit [232].

Insulin therapies

Morning administration of intermediate-acting basal human insulin may closely fit the glucose excursion induced by a single morning dose of oral steroid. Basal insulin analogues may be appropriate if hyperglycaemia is present for more prolonged periods. However, care should be taken to identify and protect against hypoglycaemia overnight and in the early morning if long-acting insulin analogues are used in this context. In those taking multiple steroid doses per day, a basal bolus regimen may be considered to be the best option.

Hospital discharge

When an individual is discharged from hospital on steroid therapy, a clear strategy for the management of hyperglycaemia or potential hyperglycaemia, and the titration of therapy to address the hyperglycaemia, should be communicated to the community diabetes team (if available) and primary care team. Individuals commenced on steroids in hospital and discharged after a short stay with the intention of continuing high-dose steroids should receive standard education regarding diabetes, encompassing the risks associated with hyper- and hypoglycaemia, such as dysglycaemia-related symptoms on which to seek advice.

If steroids are discontinued prior to discharge, and hyperglycaemia persists, then capillary blood glucose (CBG) testing should be continued on discharge until normoglycaemia returns or until a definitive test for diabetes is undertaken (HbA_{1c}, fasting glucose, or oral glucose tolerance test). If steroid treatment is ceased in hospital and CBG tests are in the normal range, then post-discharge testing is not recommended. A definitive test for diabetes should still be undertaken at least six weeks after steroid cessation.

Steroid treatment in end-of-life care

People with diabetes at the end stages of life have a unique set of clinical needs (Chapter 73). Steroid therapy is frequently used in palliative care for symptom control, usually as dexamethasone or prednisolone/prednisone. The hyperglycaemia associated with once-daily steroid therapy can often be managed by morning administration of a long-acting sulfonylurea, or morning intermediate-acting basal human insulin. However, if steroids are taken twice daily, it is probable that an alternative approach will be needed. Twice-daily short-acting sulfonylurea or isophane insulin can be effective, but there is a risk of early-morning hypoglycaemia. If hypoglycaemia is a concern, a once-daily long-acting insulin analogue given in the morning may be a safer, less complex regimen, especially for those new to insulin.

Short-term courses (<3 days) of steroids may only require closer CBG testing, but longer courses will require a review of glucose-lowering therapy and may result in a switch from oral agents to insulin. In the latter situation, an intermediate-acting basal human insulin given once daily could be considered. In those without a diagnosis of diabetes prior to the commencement of steroids, CBG testing and patient and carer education should be undertaken.

Hospital readmission

Readmission for those with diabetes is common, with hypoglycaemia and hyperglycaemia during acute hospital admission being risk factors [51]. Work has been done to identify what interventions are available to minimize the risk of readmission, which include the provision of specialist diabetes teams, whole-system embracement of recognition of the need to improve diabetes during hospitalization with a hospital-wide approach, continuous quality improvement programmes, and good communications between secondary and primary care on discharge [233].

Foot care

In the UK, the diabetic foot remains the commonest cause for a diabetes-specific acute hospital admission [103], and it was estimated that in 2014–2015 ~£1 in every £110 spent by the NHS in England was on diabetes-related foot disease [234], much of this on in-hospital care (Chapter 53). A multidisciplinary foot team, including a specialist podiatrist, diabetologist, vascular and orthopaedic surgeon, interventional radiologist, tissue viability nurse, microbiologist, DSN/CDE, and orthoptist, leads to better outcomes [235–237]. Specialist diabetes podiatrists provide the best value when considering admission avoidance, reducing length of hospital stay, and lowering amputation rates [238, 239].

The general principles for foot care in people with diabetes should apply to all admissions, not just those with active foot disease. These measures include taking a specific foot history and an inspection of the feet, looking for evidence of neuropathy, ischaemia, ulceration, inflammation, and/or infection, deformity, or Charcot neuroarthropathy. It is important to take the shoes, socks, and any dressings off the feet to inspect any underlying wounds, ensuring that pressure areas are healthy. The feet should be inspected daily during the hospital stay and any new problems should be managed in conjunction with the specialist diabetes foot multidisciplinary team.

Conclusions

People with diabetes are twice as likely to be admitted to hospital and stay twice as long as those without diabetes. They have worse outcomes and a poorer experience than those without diabetes. Given the large numbers of people with diabetes in hospital, and the considerable excess costs associated with their care, diabetes inpatient care is now being taken more seriously. However, although there is a wealth of evidence that specialist inpatient diabetes teams reduce length of stay, reduce errors in prescribing, and improve the patient experience and clinical outcomes, many institutions still lack teams specializing in inpatient diabetes.

There are numerous national and international guidelines that should make the inpatient care of people with diabetes easier to achieve. Much work remains to be done to provide more evidence to substantiate the consensus opinions within the guidelines, but as more evidence accrues showing which interventions work, the excess morbidity and mortality seen in this cohort of patients should reduce to equal those of individuals without diabetes. Until more evidence is available, it remains incumbent on those delivering the care to ensure that an attitude of nihilism is avoided – *the absence of evidence does not mean the absence of effect*. All attempts should be made to achieve suitable glycaemic levels, while avoiding symptomatic hyperglycaemia or debilitating hypoglycaemia.

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40 Hypoglycaemia in Diabetes

Ahmed Iqbal[1], Elaine Y.K. Chow[2,4,5,6], Timothy W. Jones[3], and Simon R. Heller[1]

[1] Department of Oncology and Metabolism, The Medical School, University of Sheffield, Sheffield, UK
[2] Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong SAR, China
[3] Department of Endocrinology and Diabetes, Perth Children's Hospital and Telethon Kids Institute, Perth, Western Australia, Australia
[4] Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, SAR, China
[5] Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, SAR, China
[6] Phase 1 Clinical Trial Centre, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, SAR, China

Key points

- Iatrogenic hypoglycaemia is a key limiting factor in the glycaemic management of diabetes. It occurs during treatment with a sulfonylurea, a glinide, or insulin.
- The key physiological defences against falling plasma glucose concentrations are decrements in insulin and increments in glucagon and epinephrine. The behavioural defence is carbohydrate ingestion prompted by symptoms that are the result of both sympathetic neural activation and neuroglycopenia.
- Hypoglycaemia in diabetes is the result of therapeutic hyperinsulinaemia. As glucose levels fall, increments in glucagon are lost because of β-cell failure in type 1 diabetes and advanced type 2 diabetes. In that setting, attenuated increments in epinephrine cause the syndrome of defective glucose counter-regulation.
- Attenuated increments in sympathetic neural activity largely bring about the syndrome of impaired awareness of hypoglycaemia. The failure to recognize impending hypoglycaemia is largely because the glucose threshold for sympathoadrenal activation falls below that for cognitive impairment.
- The main causes of defective glucose counter-regulation and impaired awareness of hypoglycaemia in diabetes include duration of diabetes, residual β-cell reserve, repeated episodes of hypoglycaemia, antecedent exercise, or sleep.
- Impaired awareness of hypoglycaemia and reduced sympathoadrenal activation are in part reversible in many individuals with diabetes. This may result from as little as 2–3 weeks' scrupulous avoidance of hypoglycaemia. Running high glucose levels does not provide additional benefit and is unnecessary.
- The risk factors for hypoglycaemia are related to this pathophysiology and include both relative and absolute therapeutic insulin excess, complete endogenous insulin deficiency, a history of severe hypoglycaemia, impaired awareness of hypoglycaemia, antecedent exercise, sleep, alcohol, and medication.
- This pathophysiology explains why the incidence of iatrogenic hypoglycaemia increases over time in type 2 diabetes, approaching that in type 1 diabetes. Most episodes of hypoglycaemia occur in people with type 2 diabetes, reflecting the larger numbers affected by type 2 diabetes globally.
- Minimizing the risk of iatrogenic hypoglycaemia requires acknowledging the problem, educating and empowering people with diabetes to effectively self-manage while applying the principles of flexible intensive insulin therapy, and addressing the risk factors. This includes agreeing individualized glucose targets, taking into account age, life expectancy, comorbidities, and the wishes of the person with their diabetes.
- Advances in diabetes technology including insulin analogues, continuous glucose monitoring, insulin pumps, and hybrid closed-loop systems have considerable potential to reduce hypoglycaemic risk. They appear more effective when combined with education that teaches effective self-management.
- Some individuals continue to experience recurrent severe hypoglycaemia despite structured education and the use of technology. Specifically designed psycho-educational approaches may offer a useful additional option.
- Maintenance of individualized glycaemic targets that can be accomplished safely in a given individual at a given stage of their diabetes journey is in the person's best interest. Concerns about hypoglycaemia should not be an excuse for suboptimal glycaemic management.

Overview of the clinical problem

Iatrogenic hypoglycaemia is one of the main limiting factors in the glycaemic management of diabetes [1]. It causes negative biological, psychological, and social consequences in most people with type 1 diabetes and in many with advanced type 2 diabetes. Indeed, as well as provoking substantial morbidity, hypoglycaemia is sometimes fatal. Episodes of hypoglycaemia compromise physiological and behavioural defences against subsequent falling plasma glucose concentrations and thus induce a vicious cycle of recurrent hypoglycaemia. By preventing attainment of relative euglycaemia, hypoglycaemia deprives people with diabetes of the proven benefits of keeping close to target glucose levels.

Hypoglycaemia in diabetes is fundamentally iatrogenic, and essentially a side effect of pharmacokinetically imperfect treatments with an insulin secretagogue (e.g. a sulfonylurea or a glinide) or with exogenous insulin causing hyperinsulinaemia. This is often combined with a mismatch in the amount of carbohydrates consumed or in special situations, for example during physical exercise,

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following excessive alcohol, or in groups that are particularly vulnerable, such as during pregnancy, at the extremes of age, in people with impaired awareness of hypoglycaemia, and those with comorbidities such as hepatic or renal impairment. Thus, hypoglycaemia is typically the net result of relative or absolute therapeutic insulin excess and compromised physiological and behavioural defences against falling plasma glucose [1].

In this chapter, we first explore physiological homeostatic mechanisms that prevent hypoglycaemia through glucose counter-regulation, before discussing specific acquired defects of glucose counter-regulation in diabetes, which provides an insight into risk factors for hypoglycaemia. We then discuss the size of the clinical problem followed by the biological impact of hypoglycaemia, with a specific focus on both neurological and cardiovascular consequences. Finally, we discuss hypoglycaemia in children and adolescents, including how hypoglycaemia can be approached in clinical practice, prior to providing an overall perspective on where additional research is required to address current and future needs of people with diabetes.

Hypoglycaemia and the brain

The brain relies on glucose as an obligate oxidative fuel under physiological conditions and, despite the average brain only constituting ~2% of total body weight, cerebral function accounts for 20% of whole-body glucose utilization [1–4]. The brain is almost entirely dependent on a continuous supply of glucose from the circulation for normal function. This is because it cannot synthesize glucose, utilize physiological concentrations of circulating non-glucose fuels such as amino acids, ketones, and lactate effectively, or store more than a few minutes' supply as glycogen [1,5]. This requires the plasma glucose concentration to be maintained within a tight homeostatic range to allow facilitated diffusion of sufficient glucose via glucose transporters (GLUT) across the blood–brain barrier (GLUT1) and into neurones (GLUT3) to maintain critical cerebral function. Hypoglycaemia of sufficient depth causes functional brain failure through disruption in adenosine triphosphate (ATP) and creatine phosphate metabolism, two key substrates for brain function [3,6]. Perturbations in cerebral function are initially reversible; however, with severe prolonged hypoglycaemia there is complete depletion of ATP and creatine phosphate, which can cause permanent cerebral damage and even death [3,6]. This explains both the vulnerability of individuals to hypoglycaemia and the array of defences that have evolved as a stress response to maintain near-normal plasms glucose concentrations.

Responses to hypoglycaemia

Falling plasma glucose concentrations cause a sequence of responses in individuals without diabetes termed *counter-regulatory responses* (opposing the regulatory effects of insulin) (Figure 40.1) [1,7–11]. The first physiological response, which occurs as plasma glucose concentrations decline, is a decrease in insulin secretion followed by release of glucagon and epinephrine, which increase endogenous glucose concentrations by stimulating gluconeogenesis and glycogenolysis (Figure 40.2). Lower plasma glucose levels cause a more intense sympathoadrenal (sympathetic neural and adrenomedullary) response that reduces peripheral glucose utilization and inhibits insulin secretion, in addition to triggering symptoms that prompt a behavioural response and ingestion of food. Raised cortisol and growth hormone concentrations stimulate gluconeogenesis and reduce peripheral glucose utilization, but since subsequent increases in blood glucose lag in time, these responses are less

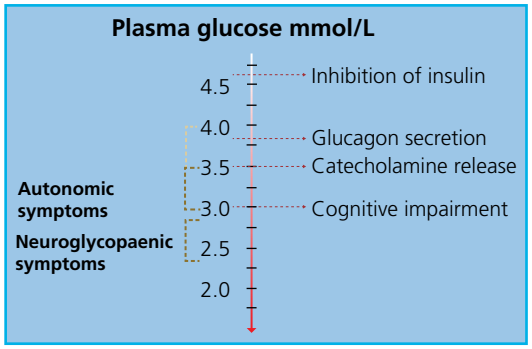

Figure 40.1 Hierarchical counter-regulatory responses to hypoglycaemia. Source: Created by A. Iqbal in Biorender.com.

relevant in acute counter-regulation of hypoglycaemia [13]. Even lower plasma glucose concentrations cause functional brain failure, which is on a clinical continuum ranging from deficits in executive function to coma and even death [3].

Clinical manifestations of hypoglycaemia

The symptoms and signs of hypoglycaemia are not specific [10,14]. Thus, in clinical practice it can be helpful to evaluate hypoglycaemia using Whipple's triad:

- Symptoms, signs, or both, consistent with hypoglycaemia.
- A low, reliably measured plasma glucose concentration.
- Resolution of those symptoms and signs after the plasma glucose is raised.

Symptoms of hypoglycaemia can be broadly categorized into neuroglycopenic and neurogenic symptoms. Neuroglycopenic symptoms occur as a result of impaired cerebral function and include cognitive impairment, loss of concentration, confusion, behavioural changes, and psychomotor abnormalities and, at lower plasma glucose concentrations, seizures and coma [1,3,10,14]. Neurogenic symptoms occur in response to activation of both the sympathetic (palpitations, tremulousness, and arousal/anxiety) and parasympathetic (sweating, hunger, and paraesthesia) components of the autonomic nervous system in response to hypoglycaemia [10,14]. Central mechanisms may also be involved in some of the latter symptoms, such as hunger that prompts a behavioural response to consume food [15]. Awareness of hypoglycaemia is at least in part the result of the perception of neurogenic symptoms [10], which are more prominent at the diagnosis of diabetes, but with time neuroglycopenic symptoms become more prominent.

Signs of hypoglycaemia include pallor and diaphoresis, the result of adrenergic cutaneous vasoconstriction and cholinergic activation of sweat glands, respectively [1]. Neuroglycopenic manifestations are often observable and those affected may complain of confusion or loss of concentration.

Counter-regulation during hypoglycaemia

Given the near-total dependence of the brain on a normal and stable systemic glucose concentration and the serious consequences of hypoglycaemia on cerebral function, a tight systemic glucose balance is maintained under physiological conditions. Bidirectional fluxes in plasma glucose that could result in hypoglycaemia or hyperglycaemia are prevented. This is achieved through homeostatic regulation of endogenous glucose production, principally in the liver but also in the kidneys, and this is balanced with peripheral glucose utilization by skeletal muscle [1,6]. Insulin plays a key role in regulating endogenous glucose production and peripheral

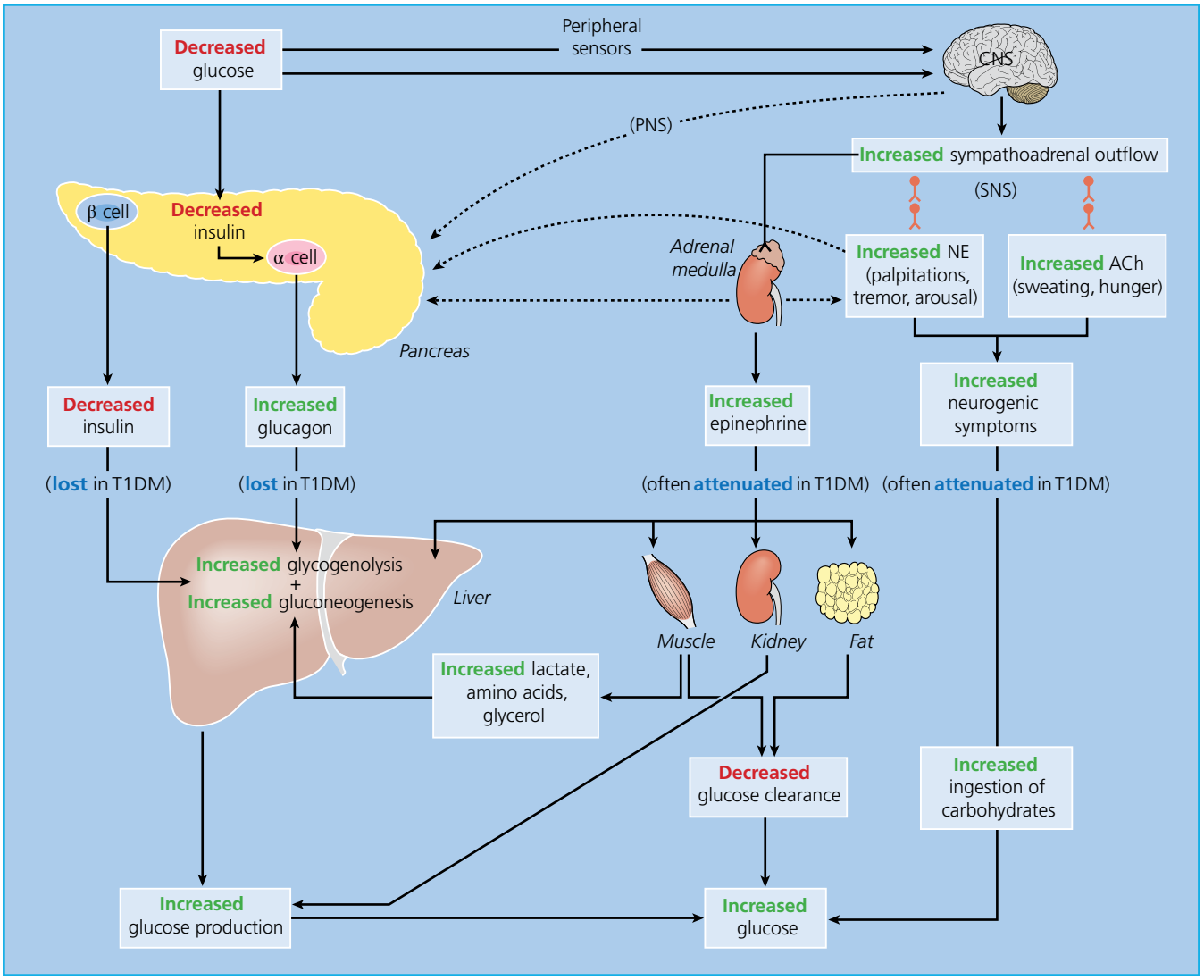

Figure 40.2 Physiological and behavioural defences against hypoglycaemia in humans. ACh, acetylcholine; α cell, pancreatic islet α cell; β cell, pancreatic islet β cell; NE, norepinephrine; PNS, parasympathetic nervous system; SNS, sympathetic nervous system; T1DM, type 1 diabetes. Source: Cryer 2006 [12]. Reproduced with permission from the American Society for Clinical Investigation.

glucose utilization in non-neural tissues, although other neurotransmitters, metabolic substrates, and hormones are involved (Figures 40.1 and 40.2) [6,16].

The processes of counter-regulation that correct hypoglycaemia involve an array of hormones. Seminal contributions from experimental medicine studies from the mid-1970s to the early 1990s have established an order of relative importance within counter-regulatory hormonal responses that can be conceptualized as lines of defence against hypoglycaemia [17–20]. The first physiological defence against hypoglycaemia is a decrease in pancreatic islet β-cell insulin secretion. This occurs as plasma glucose concentrations decline below 4.7 mmol/l (85 mg/dl) (Figure 40.1) and favours increased hepatic and renal glucose production, with virtual cessation of glucose utilization by insulin-sensitive tissues such as muscle (Figure 40.2). The second physiological defence is an increase in pancreatic islet α-cell glucagon secretion. This occurs as plasma glucose concentrations fall just below 3.9 mmol/l (70 mg/dl) (Figure 40.1) and stimulates glucose release through glycogenesis and glycogenolysis (Figure 40.2). Under physiological conditions, pancreatic α cells are under tonic inhibition of intra-islet insulin [17]. During hypoglycaemic conditions, a decrease in intra-islet insulin among other β-cell secretory products, including the neurotransmitter γ-aminobutyric acid and zinc [1,21–23], signals increased glucagon secretion. Further, a secondary putative mechanism that results in increased glucagon production is through activation of both the sympathetic and parasympathetic branches of the autonomic nervous system [1,24]. As blood glucose concentrations fall further and just below the physiological range, the third physiological defence of epinephrine secretion from the adrenal medulla comes into play. This stimulates glucose release through gluconeogenesis and glycogenolysis, largely via β_2-adrenergic stimulation, as well as reducing peripheral glucose utilization by inhibiting insulin secretion via α_2-adrenergic receptors (Figure 40.2) [1,6,25]. Adrenomedullary epinephrine secretion becomes critical when glucagon is deficient. There is also a norepinephrine response to hypoglycaemia, which is largely secreted from the adrenal medulla but compared to epinephrine appears to play a less prominent role in glucose counter-regulation [14]. Additional hormones released when blood glucose levels fall between

3.6–3.9 mmol/l (65–70 mg/dl) are growth hormone and cortisol [8,9]. Collectively, these hormones induce gluconeogenesis, lipolysis, and ketogenesis over several hours and are thus less relevant to acute counter-regulation [26]. They may have an important role in initiating longer-term adaptive responses to hypoglycaemia [27].

These complex homeostatic mechanisms are chiefly controlled by the central nervous system (CNS) [6]. The evidence supporting this is primarily derived from animal studies, where direct glucose infusion into the brain to maintain euglycaemia was studied with parallel induction of peripheral hypoglycaemia [28]. In these experiments in rats, peripheral hypoglycaemia did not result in activation of glucagon and catecholamine counter-regulation. This and other studies led to the hypothesis that the ventromedial hypothalamic nucleus in the brain is a key glucose sensor for hypoglycaemia counter-regulation [28]; however, the ventromedial hypothalamic nucleus is likely to be one part of a larger glucose-sensing network in the brain [6]. Glucose-sensing neurones are highly specialized cells that employ changes in ambient glucose levels to alter their action potential, thus transducing a metabolic signal into neuronal activity [29]. Glucokinase and ATP-sensitive K^+ channels appear to be primarily involved in glucose sensing and subsequent counter-regulation [29,30]. There may also be important species differences between rodents and humans.

If these physiological defences fail to abort an episode of developing hypoglycaemia, lower plasma glucose concentrations cause a more intense sympathoadrenal response that causes neurogenic symptoms and is primarily driven by sympathetic neural activation as opposed to adrenomedullary discharge (Figure 40.2) [14]. These symptoms cause awareness of hypoglycaemia that prompts the behavioural defence of carbohydrate ingestion. Physiological responses act in concert to prevent hypoglycaemia in healthy people without diabetes, but are typically compromised in people with type 1 diabetes and those with advanced (i.e. absolutely endogenous insulin-deficient) type 2 diabetes (Figure 40.2) [1].

Pathophysiology of glucose counter-regulation in diabetes

Insulin excess

Absolute or relative therapeutic hyperinsulinaemia is a key factor in producing iatrogenic hypoglycaemia [1]. Whether any given episode of therapeutic hyperinsulinaemia results in clinically significant hypoglycaemia in people with diabetes, however, is also determined by the integrity of hormonal and behavioural mechanisms that ordinarily constitute the counter-regulatory defence. Counter-regulatory deficiencies in diabetes are not a binary 'present or absent' phenomenon, but exist on a continuum that is influenced by several factors. Since some of these impairments appear to be functional, this implies they may be reversible (Figure 40.2; Table 40.1) [27,32,33].

Defective glucose counter-regulation

Insulin

Individuals with fully developed (minimal residual β-cell function) type 1 diabetes and advanced insulin-treated type 2 diabetes are unable to self-regulate endogenous insulin secretion in response to falling plasma glucose concentrations (Table 40.1) [34]. This compromises the first counter-regulatory defence against hypoglycaemia, as therapeutic delivery of insulin or sulfonylureas and related medication results in unregulated hyperinsulinaemia [21]. Hyperinsulinaemia promotes glucose lowering through peripheral glucose uptake in the liver, skeletal muscle, and adipose tissue in addition to suppressing gluconeogenesis and inhibiting lipolysis, which generates alternate fuels [27]. In addition, insulin inhibits pancreatic α-cell glucagon release, partly through direct local action in the pancreas [35] but also through central modulation in the ventromedial hypothalamic nucleus [36].

Table 40.1 Responses to falling plasma glucose concentrations in humans.

Plasma glucose	Individuals	Plasma		
		Insulin	Glucagon	Epinephrine
↓	No-diabetes	↓	↑	↑
↓	Type 1 diabetes[a]	No ↓	No ↑	Attenuated ↑
↓	Early type 2 diabetes	↓	↑	↑
↓	Late type 2 diabetes[a]	No ↓	No ↑	Attenuated ↑

[a] These alterations account for the appearance of defective glucose counter-regulation and impaired awareness of hypoglycaemia in people with type 1 diabetes and late type 2 diabetes.
Source: Reproduced by permission from Cryer 2008 [31].

Glucagon

In the absence of the ability to *switch off* endogenous insulin in response to falling glucose concentrations, people with diabetes have to rely on glucagon secretion, which is the second line of physiological defence against hypoglycaemia. Glucagon plays a primary role in opposing the glucose-lowering effects of insulin during hypoglycaemia, accounting for ~40% of glucose recovery [37]. However, impaired glucagon responses to hypoglycaemia are apparent as early as within the first year of diagnosis in type 1 diabetes [38] and are significantly diminished in most people within five years after diagnosis (Table 40.1) [39]. Glucagon and other counter-regulatory responses to hypoglycaemia are less extensively studied in type 2 diabetes, but limited evidence suggests that in type 2 diabetes glucagon responses are initially either elevated or modestly reduced (Table 40.1) [40–43], but become gradually impaired [33,44–46].

An interesting phenomenon observed in clinical practice is that some individuals with type 2 diabetes, especially those with suboptimal metabolic management and thus relatively high ambient plasma glucose concentrations, report symptoms suggestive of counter-regulation occurring at normal glucose values. Furthermore, experimental data suggest that the threshold for activation of counter-regulatory responses to hypoglycaemia may be reset to normal glucose values in some individuals with type 2 diabetes [41]. Loss of a glucagon response results in significantly reduced glycogenolysis and gluconeogenesis and increases the risk of severe hypoglycaemic episodes [27,47]. Mechanisms that lead to loss of α-cell glucagon release in diabetes are not fully understood. Several mechanistic studies have been performed in animals, which may not directly apply to the human condition due to species differences in pancreatic physiology. It appears, however, that the α-cell defect, at least in those with type 1 diabetes, is specific to hypoglycaemia, as α-cell stimulation with amino acids such as arginine results in an intact glucagon response [17]. The α-cell glucagon

release appears to be impaired on account of a functional as opposed to a structural defect, raising the theoretical possibility of interventions that may re-enable glucagon secretion in response to a hypoglycaemic stimulus.

One plausible explanation for the loss of glucagon response to hypoglycaemia in type 1 diabetes and advanced type 2 diabetes is β-cell failure, as described in the *intra-islet* hypothesis [21,33]. As intra-islet insulin, among other β-cell secretory products, regulates α-cell glucagon secretion in response to hypoglycaemia [17], with progressive β-cell failure either through T-cell–mediated autoimmune destruction in type 1 diabetes or gradual β-cell loss with advancing type 2 diabetes, the absence of intra-islet insulin signalling results in a loss of the glucagon response to hypoglycaemia [48]. Heller et al. were the first to explore the intra-islet hypothesis in humans and contrasted this with animal data [49]. They studied glucagon responses in healthy volunteers who underwent two hypoglycaemic clamps, one with intravenous tolbutamide infusion to stimulate high portal insulin concentrations, and compared this with a standard intravenous insulin infusion clamp with an equivalent hypoglycaemic nadir. They showed a reduced glucagon response to tolbutamide-induced hypoglycaemia where portal insulin concentrations were high, suggesting that intra-islet insulin signalling contributes to regulation of glucagon release during hypoglycaemia in humans [49].

Other early experimental data that support the intra-islet hypothesis were a demonstration of impaired glucagon secretion during hypoglycaemia, closely mirroring a decline in C-peptide levels (a marker of endogenous β-cell function) in people with insulin-treated diabetes [50]. In a more recent study, when people with insulin-treated type 2 diabetes were compared with those on oral hypoglycaemic agents only, there was no difference in the peak glucagon response during a hypoglycaemic clamp [51]. However, this was almost certainly because even insulin-treated participants had relatively preserved β-cell function (mean C-peptide 1000 pmol/l). A similarly designed study examined glucagon responses to experimental hypoglycaemia in people with type 2 diabetes treated with oral hypoglycaemic agents and compared people treated with insulin and lower mean basal C-peptide values (mean C-peptide insulin-treated group 364 pmol/l vs mean C-peptide oral hypoglycaemic group 1026 pmol/l) [33]. Here, mean glucagon responses following 60 minutes of experimental hypoglycaemia were significantly higher in the oral hypoglycaemic group compared to the insulin-treated group. Further, recent observational studies in both type 1 diabetes and insulin-treated type 2 diabetes suggest that the incidence of continuous glucose monitoring (CGM)–recorded hypoglycaemia is significantly lower in those with preserved C-peptide levels, inferring an intact glucagon response and lending credence to the intra-islet hypothesis [52,53].

Catecholamines

With both the first and second physiological defences against hypoglycaemia being lost, people with diabetes have to rely on the catecholamine (principally epinephrine) response to hypoglycaemia – the third line of defence. Notably, when the glucagon response is poor, hepatic glucose production during hypoglycaemia and exercise is significantly modulated by catecholamines, highlighting the critical nature of this *fail safe* [27,54,55]. However, in those with type 1 diabetes and advanced type 2 diabetes, the epinephrine response to hypoglycaemia is progressively attenuated (Figure 40.3; Table 40.1) [1,32,33,39]. An attenuated adrenomedullary epinephrine response

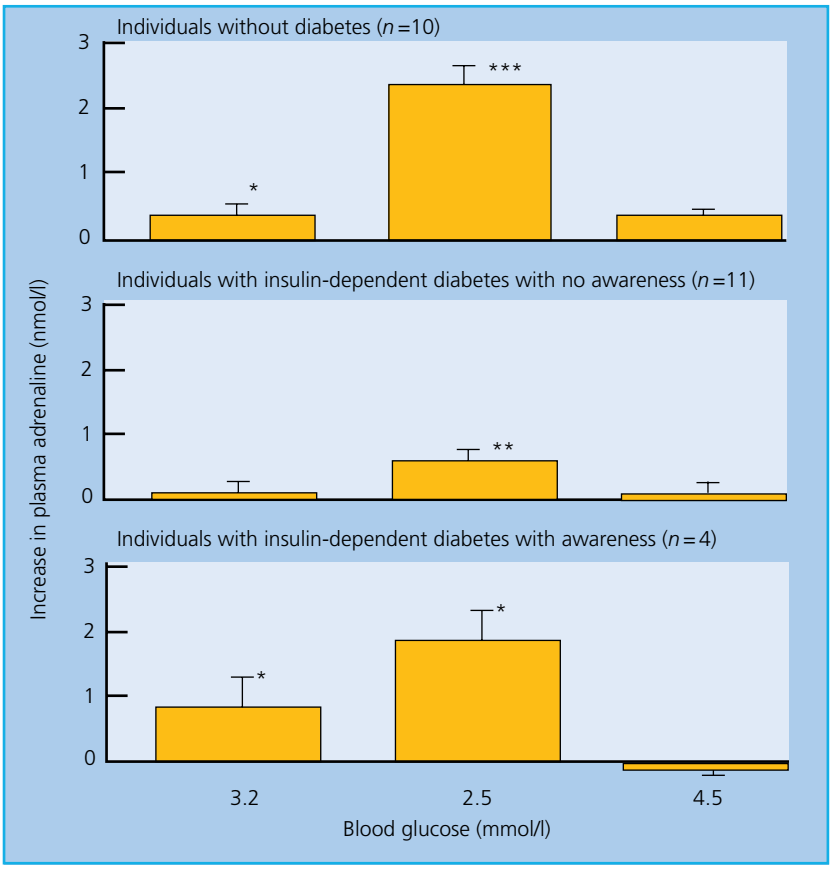

Figure 40.3 Mean (± standard error [SE]) plasma epinephrine concentrations during stepped hyperinsulinaemic hypoglycaemic glucose clamps in 10 individuals without diabetes and 15 individuals with insulin-dependent diabetes (n = 4 with intact awareness of hypoglycaemia and n = 11 with reduced awareness of hypoglycaemia symptoms). Source: Heller et al. 1987 [56]. Reproduced with permission from the Lancet.

together with an absent glucagon response is associated with a 25-fold [47] or greater [57] increase in the risk of severe hypoglycaemia in type 1 diabetes. In addition, a diminished adrenal epinephrine response is a marker for an attenuated autonomic response to hypoglycaemia, including a sympathetic neural response (Table 40.1), which is primarily responsible for reduced neurogenic symptoms [14] and the clinical syndrome of impaired awareness of hypoglycaemia. The adrenal glands are regulated by the autonomic nervous system [27]. The impaired catecholamine response to hypoglycaemia in individuals with type 1 diabetes and advanced type 2 diabetes arises mainly through an altered sympathetic drive, with a gradual shifting of the glycaemic threshold for activation to lower glucose values [58]. There is no structural defect in the secretory apparatus within the adrenal medulla, however, given that a catecholamine response to alternate stimuli such as exercise remains intact [55, 58].

Overall, the pathophysiology of glucose counter-regulation is similar in type 1 diabetes and advanced (i.e. absolutely endogenous insulin deficiency) type 2 diabetes, albeit with different time courses (Table 40.1) [1, 32, 33]. The pathogenesis of an episode of iatrogenic hypoglycaemia involves therapeutic hyperinsulinaemia, resulting in falling plasma glucose concentrations and loss of the appropriate reduction in insulin and compensatory secretion of glucagon. Each episode of hypoglycaemia, in turn, reduces the sympathoadrenal responses to subsequent hypoglycaemia. Because β-cell failure, which causes loss of both insulin and glucagon responses [1, 32, 33], occurs rapidly in type 1 diabetes but more insidiously in type 2 diabetes, the syndromes of defective glucose counter-regulation and impaired awareness of hypoglycaemia develop early in type 1 diabetes but later in type 2 diabetes. This temporal pattern of compromised glycaemic defences explains why iatrogenic hypoglycaemia becomes progressively more frequent as individuals approach the insulin-deficient end of the spectrum of type 2 diabetes.

Impaired awareness of hypoglycaemia

Important work by Heller and Cryer in the early 1990s showed that in healthy volunteers, a single episode of hypoglycaemia is sufficient to attenuate sympathoadrenal (and glucagon) responses to subsequent hypoglycaemia [20]. This phenomenon, subsequently replicated in those with type 1 diabetes (Figures 40.4 and 40.5) [32, 59] and type 2 diabetes [60], reduces an individual's ability to perceive the onset of hypoglycaemia symptoms [60]. Hypoglycaemia of greater depth [61], longer duration [62], and higher frequency [63, 64] results in a greater attenuation of counter-regulatory responses to subsequent hypoglycaemia [27]. It is unclear, however, if the progressive impairment in sympathoadrenal responses that occurs in diabetes of increasing duration is entirely due to repeated hypoglycaemia [34]. Clinical experience indicates that many individuals with longstanding insulin-treated diabetes have a diminished ability to perceive the symptoms of acute hypoglycaemia. No holistic definition for the clinical syndrome of impaired hypoglycaemia awareness exists, but it is recognized that absolute unawareness is rare and thus the term *hypoglycaemia unawareness* has been replaced with *impaired awareness of hypoglycaemia* [34].

Scales developed by Gold [65] and Clarke [66] are two tools used in routine clinical practice to identify impaired awareness of hypoglycaemia in type 1 diabetes, but they have limitations. Recent studies have used a Gold score of ≥4 to define impaired awareness of hypoglycaemia [67, 68]; however, there is significant variation in how impaired awareness of hypoglycaemia is defined in older studies, making it challenging to draw meaningful comparisons between populations, especially where duration of treatment with insulin differs. Where there is broad consistency in definitions of impaired awareness of hypoglycaemia, the reported prevalence is ~25% in type 1 diabetes, rising to ~50% after 25 years or more of treatment [69–71]. In type 2 diabetes, the prevalence of impaired awareness of hypoglycaemia is ~8–10% [72, 73], with the prevalence being higher in insulin-treated type 2 diabetes [72]. This is intuitive, as the duration of insulin treatment is a key predictor of rates of severe hypoglycaemia, with higher rates reported in both type 1 diabetes and type 2 diabetes with longer treatment duration [74]. Interestingly, when individuals with type 1 diabetes and type 2 diabetes were matched for duration of treatment with insulin in one study [75], hypoglycaemia rates were comparable. This has important implications for healthcare resources around the world, since the global prevalence of type 2 diabetes is far higher, comprising 90% of all cases of diabetes [76]. Improved access to insulin together with longer life expectancies will mean that hypoglycaemia will continue to remain a significant clinical challenge [77].

Although impaired awareness of hypoglycaemia is largely the result of reduced release of the neurotransmitters norepinephrine and acetylcholine [1, 14], there is decreased β-adrenergic sensitivity, specifically reduced cardiac chronotropic sensitivity to isoproterenol, in affected individuals [78, 79]. However, vascular sensitivity to β_2-adrenergic agonism was not found to be reduced in people with impaired awareness [80]; reduced sensitivity to β-adrenergic signalling of neurogenic symptoms remains to be demonstrated in those with impaired awareness of hypoglycaemia, and it would be necessary to postulate decreased cholinergic sensitivity to explain reduced cholinergic symptoms such as sweating.

Mechanisms of counter-regulatory failure and impaired awareness

Epidemiological and mechanistic studies have shown that duration of type 1 diabetes and insulin treatment in type 2 diabetes are key contributors to deficient counter-regulation and impaired awareness of hypoglycaemia. Repeated episodes of hypoglycaemia are also fundamental to these pathological syndromes that make insulin-treated individuals so susceptible to the limitations of therapeutic insulin and other therapies.

Following the seminal studies conducted in the early 1990s, further studies showed that an episode of antecedent hypoglycaemia can attenuate counter-regulatory responses to further hypoglycaemia up to one week later [81]. Brief twice-weekly episodes of mild hypoglycaemia have a similar effect [82]. Furthermore, prior exercise [83–85] and sleep [86–88] cause diminished counter-regulation to subsequent hypoglycaemia. Prolonged effects of antecedent hypoglycaemia on diminished counter-regulation to subsequent hypoglycaemia appear to explain why tight glycaemic management with intensive insulin therapy can lead to a resetting of the glycaemic threshold at which counter-regulatory mechanisms are activated [34, 59, 89]. Thus, stimuli such as prior hypoglycaemia, sleep, and exercise can plausibly contribute to transient impaired awareness of hypoglycaemia by attenuating the sympathoadrenal and resultant neurogenic symptom responses to subsequent hypoglycaemia.

It remains unclear how these factors lead to chronic impaired awareness. Nonetheless, recurrent episodes of hypoglycaemia of sufficient depth and duration progressively blunt and impair normal counter-regulatory responses to hypoglycaemia, predisposing people with diabetes to a vicious cycle of ever more frequent hypoglycaemia episodes with a falling glycaemic threshold to activate counter-regulation (Figure 40.6) [34, 90]. Cryer has termed

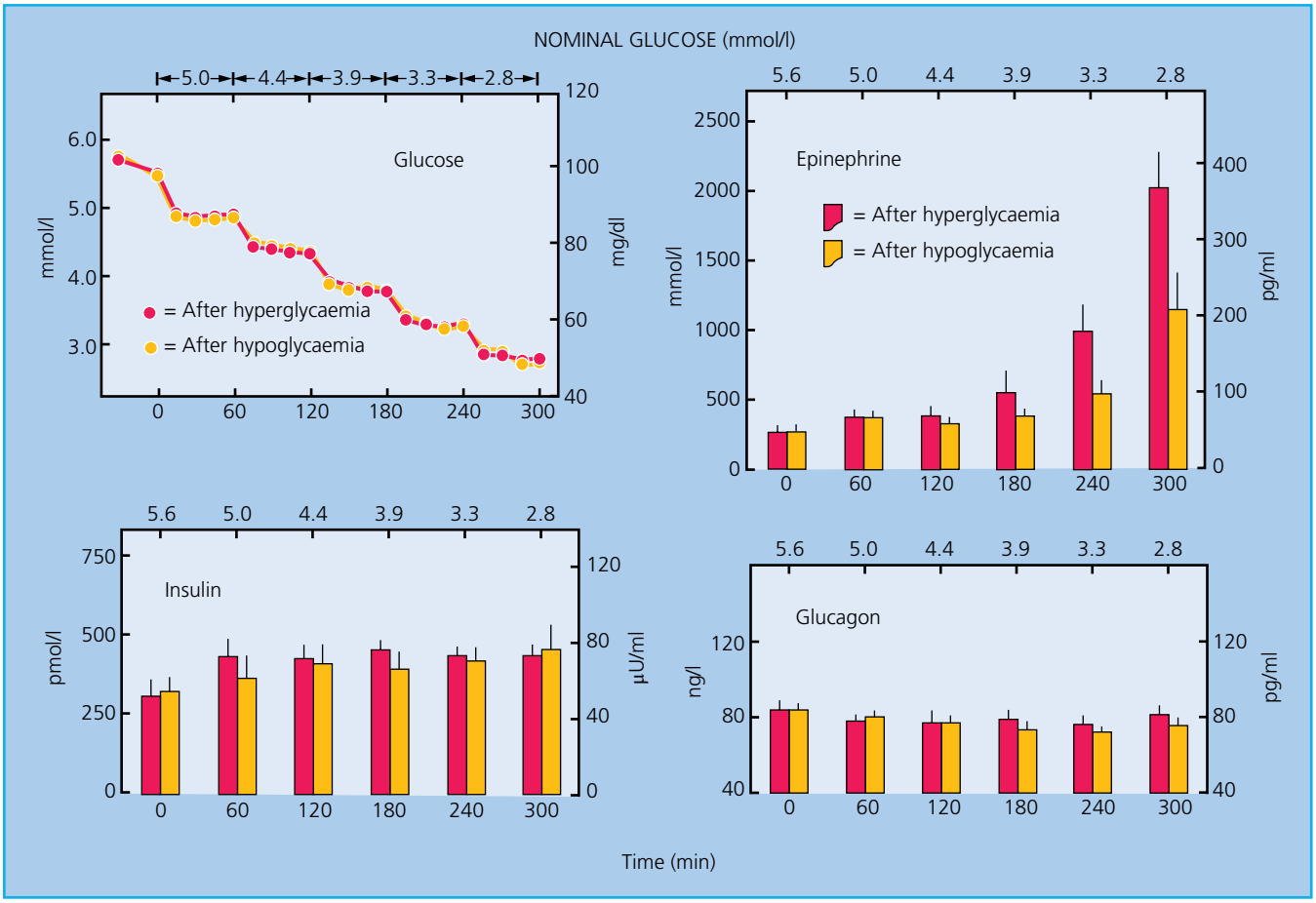

Figure 40.4 Mean (± standard error [SE]) plasma glucose, insulin, epinephrine, and glucagon concentrations during hyperinsulinaemic stepped hypoglycaemic glucose clamps in people with type 1 diabetes without classic diabetic autonomic neuropathy on mornings following afternoon hyperglycaemia (red circles and columns) and on mornings following afternoon hypoglycaemia (yellow circles and columns). Source: Dagogo-Jack et al. 1993 [32]. Reproduced with permission from the American Society for Clinical Investigation.

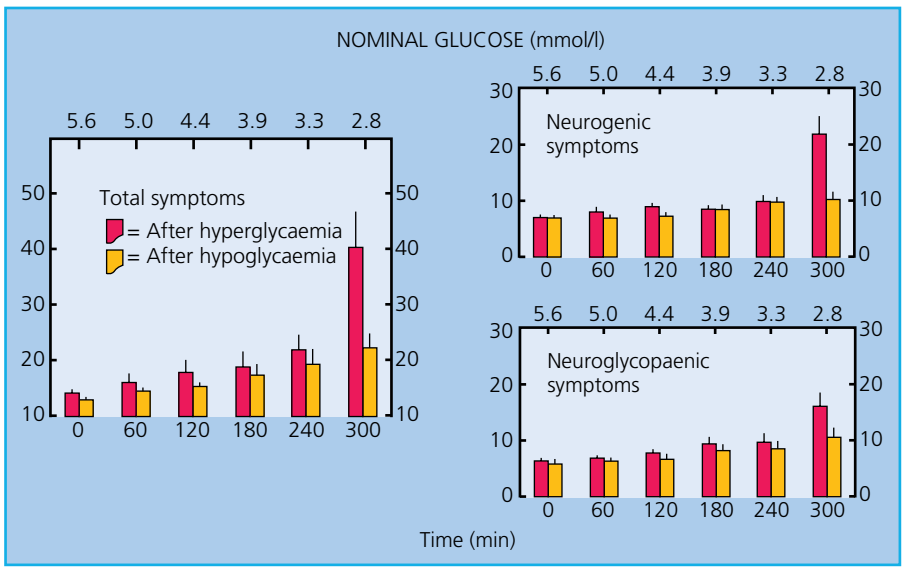

Figure 40.5 Mean (± standard error [SE]) total, neurogenic, and neuroglycopaenic symptom scores during hyperinsulinaemic stepped hypoglycaemic clamps in people with type 1 diabetes without classic diabetic autonomic neuropathy on mornings following afternoon hyperglycaemia (red columns) and on mornings following afternoon hypoglycaemia (yellow columns). Source: Dagogo-Jack et al. 1993 [32]. Reproduced with permission from the American Society for Clinical Investigation.

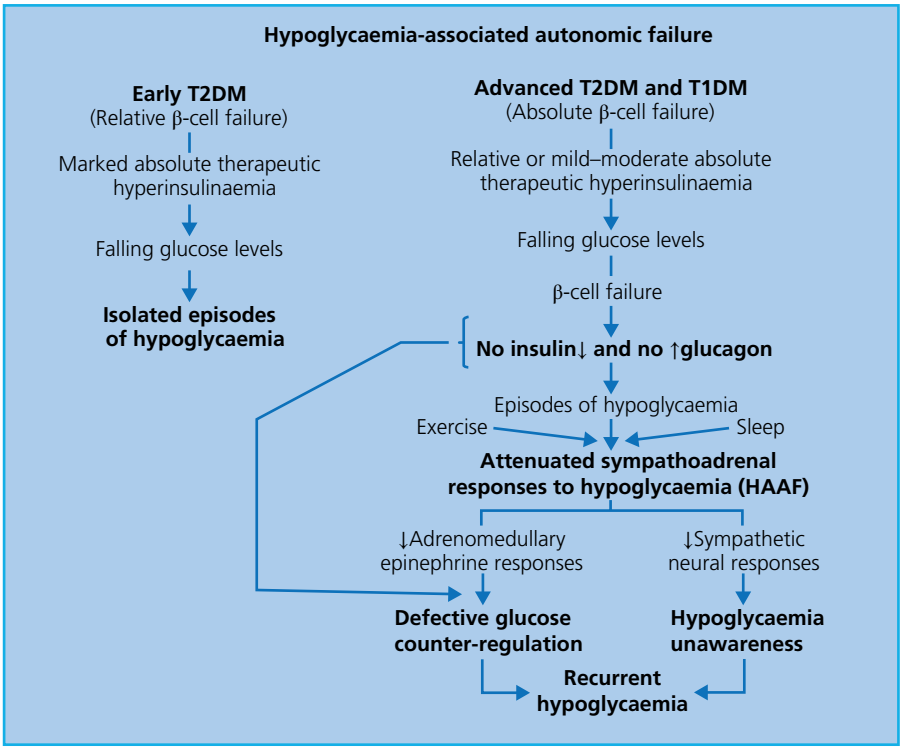

Figure 40.6 Hypoglycaemia-associated counter-regulatory impairment in the pathogenesis of iatrogenic hypoglycaemia in diabetes. HAAF, hypoglycaemia-associated autonomic failure; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

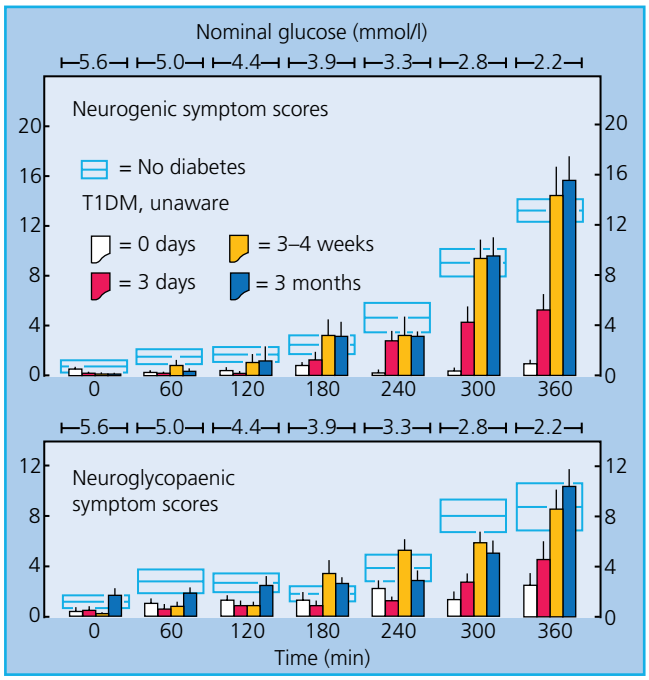

Figure 40.7 Mean (± standard error [SE]) neurogenic and neuroglycopenic symptom scores during hyperinsulinaemic stepped hypoglycaemic clamps in individuals without diabetes (open rectangles) and in people with type 1 diabetes (T1DM; columns) at baseline (0 days), after three days of inpatient strict avoidance of hypoglycaemia, and after three to four weeks and three months of outpatient scrupulous avoidance of hypoglycaemia. Source: Dagogo-Jack et al. 1994 [94]. Reproduced with permission from the American Diabetes Association.

this phenomenon *hypoglycaemia-associated autonomic failure* in diabetes [91]. This is a dynamic functional disorder that is distinct from classic diabetic autonomic neuropathy [1,34], a common neuropathic complication of diabetes. While there is no failure of the autonomic system in hypoglycaemia-associated autonomic failure, an attenuated sympathoadrenal response to a given level of hypoglycaemia, a key feature of hypoglycaemia-associated autonomic failure, is common to diabetic autonomic neuropathy [92,93]. However, since structural autonomic neuropathy is generally only observed in individuals with a long duration of diabetes, it is difficult to assess the additional contribution of autonomic neuropathy to counter-regulatory failure. A more accurate term would be hypoglycaemia-associated counter-regulatory impairment, to distinguish it from impairment secondary to other factors such as treatment duration, exercise, and sleep; nevertheless, the term hypoglycaemia-associated autonomic failure is now used widely.

The clinical impact of hypoglycaemia-associated counter-regulatory impairment is well established in type 1 diabetes [32,82,94–98]. Recent antecedent hypoglycaemia, even asymptomatic nocturnal hypoglycaemia, reduces epinephrine, symptomatic, and cognitive responses to a given level of subsequent hypoglycaemia [98], reduces detection of hypoglycaemia in the clinical setting [82], and reduces defence against hyperinsulinaemia [32] in type 1 diabetes. Perhaps the most compelling evidence to support the concept of hypoglycaemia as a cause of counter-regulatory impairment is the finding, initially by three independent research teams [94–98], that as little as 2–3 weeks of scrupulous avoidance of hypoglycaemia reverses impaired awareness of hypoglycaemia (Figure 40.7) and improves the attenuated epinephrine component of defective glucose counter-regulation in most affected individuals.

People with advanced type 2 diabetes are also at risk for acquired counter-regulatory impairment [33]. Glucagon responses to hypoglycaemia are lost [33], as they are in type 1 diabetes. Furthermore, the glycaemic thresholds for sympathoadrenal and symptomatic (among other) responses to hypoglycaemia are shifted to lower plasma glucose concentrations by recent antecedent hypoglycaemia [33], as they are in type 1 diabetes.

There are three recognized causes of counter-regulatory failure, each of which leads to attenuated sympathoadrenal and symptomatic (among other) responses to a given level of hypoglycaemia [1]. Antecedent hypoglycaemia related counter-regulatory failure [20, 32, 33] led the concept. Exercise-related counter-regulatory failure [84–86] is exemplified by late post-exercise hypoglycaemia, which typically occurs 6–15 hours after strenuous exercise and is often nocturnal [99, 100]. Sleep-related counter-regulatory failure [87–89] is the result of further attenuation of the sympathoadrenal response to hypoglycaemia during sleep. Sleeping individuals are therefore much less likely to be awakened by hypoglycaemia than individuals without diabetes [87, 89]. There may well be additional, as yet unrecognized, functional, and therefore potentially reversible, causes of hypoglycaemia-associated counter-regulatory impairment [1]. In addition, there may be a structural component [1].

The mechanisms of counter-regulatory impaired awareness are summarized in Figure 40.8 [1]. Loss of the insulin and glucagon responses to falling plasma glucose concentrations caused by therapeutic hyperinsulinaemia is the result of β-cell failure in type 1 diabetes and advanced type 2 diabetes.

In the setting of absent insulin and glucagon responses to falling plasma glucose concentrations, attenuated sympathoadrenal responses cause both defective glucose counter-regulation and impaired awareness of hypoglycaemia. The underlying mechanism responsible for the attenuated sympathoadrenal response is poorly understood, but it is plausible that it is at the level of the brain (or the afferent or efferent components of the sympathoadrenal system) (Figure 40.8). The proposed mechanisms include the systemic mediator, brain fuel transport, and brain metabolism hypotheses, all of which have been previously reviewed [21, 101, 102].

Much of the research into the pathogenesis of counter-regulatory failure has focused on the hypothalamus, the central integrator of the sympathoadrenal responses to hypoglycaemia [102]. While the primary alteration could reside in the hypothalamus, the changes in hypothalamic function could be secondary to those in other brain regions. For example, measurements of regional cerebral blood flow with [^{15}O] water and positron emission tomography (PET) [103] indicate that hypoglycaemia activates widespread but interconnected brain regions, including the medial prefrontal cortex, the lateral orbitofrontal cortex, the thalamus, the globus pallidus, and the periaqueductal grey region. These studies also show that recent antecedent hypoglycaemia both reduces the sympathoadrenal and symptomatic responses and causes a greater increase in synaptic activity in the dorsal midline thalamus during subsequent hypoglycaemia [11]. Hence there may be a cerebral network that results in thalamic inhibition of hypothalamic activity in hypoglycaemia-associated counter-regulatory impairment (Figure 40.8) [11]. That suggestion is generically consistent with the findings of various patterns of ^{18}F-deoxyglucose uptake in people with type 1 diabetes with and without impaired awareness of hypoglycaemia [104].

More recently, Choudhary et al. have investigated brain responses to hypoglycaemia in type 1 diabetes with and without impaired awareness of hypoglycaemia [105]. Using three-dimensional pseudo-continuous arterial spin labelling (3DpCASL) magnetic resonance imaging (MRI), they demonstrated changes in cerebral blood flow in response to hypoglycaemia in brain regions involved in arousal, decision making, and reward in those with impaired awareness of hypoglycaemia. They hypothesized that changes in these neural pathways may disrupt these individuals' ability to recognize and effectively manage hypoglycaemia [105]. They extended this work by restoring awareness of hypoglycaemia in those with type 1 diabetes through enrolment on a structured education programme (Dose Adjustment for Normal Eating), specialist support, and sensor-augmented pump therapy [106]. Cerebral blood flow responses during hypoglycaemia

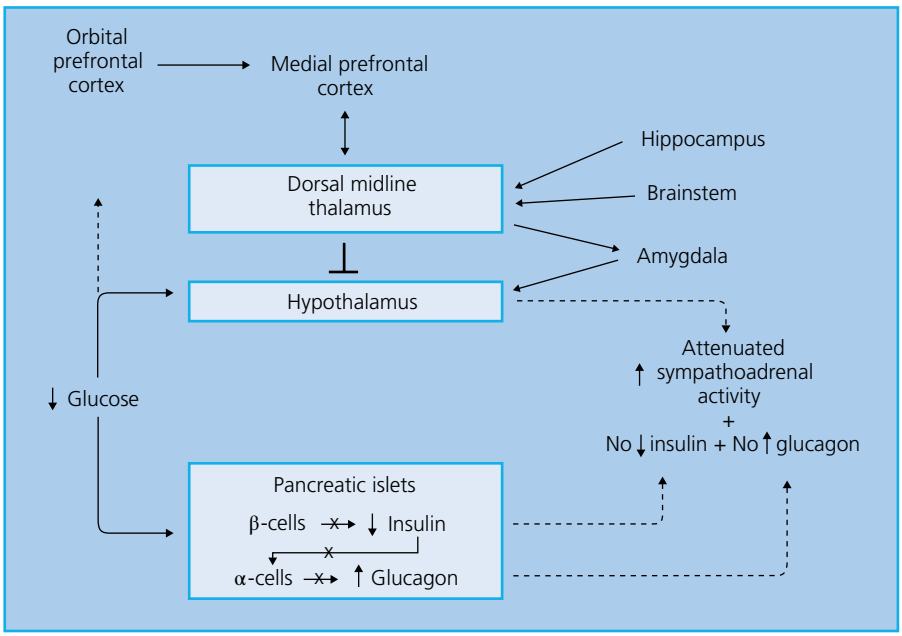

Figure 40.8 Pancreatic islet, hypothalamic, and cerebral network mechanisms of hypoglycaemia-associated autonomic failure (HAAF) in diabetes. Source: Cryer 2008 [1]. Reproduced with permission from the American Diabetes Association.

were studied pre- and post-intervention using 3DpCASL MRI. Interestingly, following restoration of hypoglycaemia awareness, increased blood flow was seen in neural pathways involved in self-awareness and decision making (anterior cingulate cortex), suggesting reversibility in brain responses lost in impaired awareness of hypoglycaemia [106]. However, brain regions involved in arousal and emotional processing (fronto-thalamic networks) were less responsive to restoration of hypoglycaemia awareness [106]. This may partly explain why some individuals with impaired awareness of hypoglycaemia never fully achieve restoration of awareness with use of structured education and diabetes technology [106].

Experimental limitations in studying the mechanisms contributing to hypoglycaemia in diabetes

It remains unclear how duration of diabetes and antecedent hypoglycaemia, the two key contributors to impaired awareness and counter-regulatory failure, interact mechanistically in causing the syndromes that underly the vulnerability of those with insulin-treated diabetes to hypoglycaemia. Most experimental work has focused on antecedent hypoglycaemia, as it is more easily reproduced in the laboratory whether in clinical experimental models or in animal studies. Since impaired awareness is increasingly observed as the duration of diabetes increases, it may reflect structural changes within the brain that prevent the reversal of sympathoadrenal failure to hypoglycaemia by avoiding further episodes. Reversal studies have shown restoration of awareness, at least in part without any improvement in rises in counter-regulatory hormones, particularly epinephrine, suggesting that sympathoadrenal responses to hypoglycaemia are still impaired [94–98].

Conversely, there are those with a long duration of diabetes who show full awareness of hypoglycaemia and still develop sweating and tremor. Have they largely avoided hypoglycaemia throughout their lives by running higher glucose levels or do they possess or have they acquired other protective mechanisms that protect against hypoglycaemia? For example, those who retain some endogenous insulin secretion in type 1 diabetes continue to exhibit a hypoglycaemic response to glucagon [107].

Another limitation in studying mechanisms of counter-regulatory failure and impaired awareness is an inability to clearly define the clinical phenotype. Some cases of impaired awareness may be almost entirely due to repeated episodes of hypoglycaemia and largely reversible (this is often seen in children), whereas others may be due to a gradual decline in hypoglycaemic warnings as their diabetes progresses due to different mechanisms that are irreversible.

These limitations may help to understand why, over 30 years after the clinical studies that described repeated hypoglycaemia as an important cause of counter-regulatory failure, we still rely on avoidance of hypoglycaemia as a treatment for impaired awareness and have not yet developed any effective pharmacological therapies that can treat or prevent it.

Risk factors for hypoglycaemia in diabetes

The risk factors for hypoglycaemia in diabetes follow directly from the pathophysiology of glucose counter-regulation. They are based on the principle that iatrogenic hypoglycaemia is typically the result of an interplay between relative or absolute therapeutic insulin excess and compromised physiological and behavioural defences against falling plasma glucose concentrations in type 1 diabetes and advanced type 2 diabetes [1, 108].

Absolute or relative insulin excess

The conventional risk factors for hypoglycaemia in diabetes are based on the premise that absolute or relative therapeutic insulin excess is the sole determinant of risk (Table 40.2) [1, 108]. Absolute therapeutic insulin excess occurs when insulin secretagogue or insulin doses are excessive, ill-timed, or of the wrong type, or when insulin clearance or metabolism is reduced, as in renal or hepatic failure. Relative therapeutic insulin excess occurs under a variety of conditions. It occurs when exogenous glucose delivery is decreased (for example, following missed or low-carbohydrate meals and during the overnight fast), when glucose utilization is increased (for example, during and shortly after exercise), when endogenous glucose production is decreased (for example, following alcohol ingestion), and when sensitivity to insulin is increased (for example, after weight loss or improved glycaemic levels and during the night). People with diabetes, their caregivers, and physicians have to work together in identifying and addressing these risk factors when the problem of iatrogenic hypoglycaemia is recognized. Overall, however, these factors likely explain only a minority of episodes of hypoglycaemia [109].

Compromised defences against hypoglycaemia

The risk factors indicative of impaired counter-regulatory responses and impaired awareness (Table 40.2) [50, 108, 110–115] include absolute endogenous insulin deficiency [50, 108, 110, 111, 113, 114]; a history of severe iatrogenic hypoglycaemia, impaired awareness of hypoglycaemia, or both; recent antecedent hypoglycaemia, prior exercise, or sleep [108, 110, 111, 115]; and intensive glycaemic therapy (i.e. lower glycated haemoglobin [HbA_{1c}], lower glycaemic targets, or both) [108, 110–115]. The degree of endogenous insulin deficiency (i.e. β-cell failure) determines the extent to which insulin levels will not decrease and glucagon levels will not increase as plasma glucose concentrations fall in response to therapeutic hyperinsulinaemia. A history of severe hypoglycaemia indicates, and that of impaired awareness of hypoglycaemia implies, a long duration of diabetes, recent antecedent hypoglycaemia, or both. The latter causes attenuated sympathoadrenal and symptomatic responses to

Table 40.2 Risk factors for hypoglycaemia in diabetes.

Relative or absolute insulin excess
1. Insulin or insulin secretagogue doses are excessive, ill-timed, or of the wrong type
2. Exogenous glucose delivery is decreased (e.g. following missed meals and during the overnight fast)
3. Glucose utilization is increased (e.g. during and shortly after exercise)
4. Endogenous glucose production is decreased (e.g. following alcohol ingestion)
5. Sensitivity to insulin is increased (e.g. in the middle of the night and following weight loss or improved glycaemic levels)
6. Insulin clearance or metabolism is decreased (e.g. with renal or liver failure)
Hypoglycaemia-associated counter-regulatory impairment
1. Absolute endogenous insulin deficiency
2. A history of severe hypoglycaemia, impaired awareness of hypoglycaemia, or both, and also recent antecedent hypoglycaemia, prior exercise, and sleep
3. Intensive glycaemic therapy (lower glycated haemoglobin [HbA_{1c}], lower glycaemic goals)

subsequent hypoglycaemia. Studies of intensive glycaemic therapy with a control group treated to a higher HbA_{1c} level consistently report higher rates of hypoglycaemia in the group treated to lower HbA_{1c} levels in type 1 diabetes [116–118] and type 2 diabetes [113, 119, 120]. The challenge in clinical practice is to allow people with diabetes to derive the benefits of intensive glycaemic management while minimizing the risk and consequences of hypoglycaemia.

Magnitude of the clinical problem of hypoglycaemia in diabetes

Diabetes is an increasingly common disease and iatrogenic hypoglycaemia affects most of those with type 1 diabetes and people with type 2 diabetes treated with insulin or secretagogues [1, 5]. Indeed, because maintenance of euglycaemia is needed over a lifetime of diabetes, the barrier of hypoglycaemia ultimately affects most people with diabetes [1, 5].

Frequency of hypoglycaemia

Hypoglycaemia is a fact of life for people with type 1 diabetes (Table 40.3) [1, 5, 110, 112, 132]. The average person has untold numbers of episodes of asymptomatic hypoglycaemia and experiences on average, around two episodes of symptomatic hypoglycaemia per week – thousands of such episodes over a lifetime of diabetes – and one or more episodes of severe, temporarily disabling hypoglycaemia, often with seizure or coma, per year. There is little evidence that this problem has abated since it was highlighted by the Diabetes Control and Complications Trial (DCCT) in 1993 [116]. For example, in 2007 the UK Hypoglycaemia Study Group [74] reported an incidence of severe hypoglycaemia that was twice that in the DCCT in people with type 1 diabetes for <5 years, and an incidence fivefold higher than that in the DCCT in those with type 1 diabetes for >15 years (Table 40.3). An incidence comparable to the latter was also found in a large observational study [112].

Overall, hypoglycaemia is less frequent in type 2 diabetes (Table 40.3) [1, 5, 73–75, 112, 115, 118, 121, 122, 124–130, 133–136], but for the pathophysiological reasons discussed, hypoglycaemia becomes progressively more frequent as people approach the insulin-deficient end of the spectrum of type 2 diabetes [1, 5, 74, 75]. Indeed, its frequency has been reported to be similar in those with type 2 diabetes and type 1 diabetes matched for duration of insulin therapy [75]. When the UK Hypoglycaemia Study Group [74] contrasted people with type 2 diabetes treated with insulin for <2 years with those treated with insulin for >5 years, they found severe hypoglycaemia prevalence rates of 7% and 25% and incidence rates

Table 40.3 Event rates for severe hypoglycaemia (that requiring the assistance of another person), expressed as episodes per 100 person-years, in insulin-treated diabetes.

Study	n	Event rate	Comment
Type 1 diabetes			
UK Hypoglycaemia Study Group 2007 [74]	57[a]	320	Prospective multicentre study
	50[b]	110	
MacLeod et al. 1993 [121]	544	170	Retrospective clinic survey, randomly selected sample
Donnelly et al. 2005 [122]	94	115	Prospective study, population-based random sample
Reichard and Pihl 1994 [118]	48	110	Clinical trial, intensive insulin group
DCCT Research Group 1993 [116]	711	62	Clinical trial, intensive insulin group
Khunti et al. 2016 [123]	8022	490	Retrospective 6 mo and 4 wk self-reported prospective multinational survey
Type 2 diabetes			
MacLeod et al. 1993 [121]	56	73	Retrospective clinic survey, randomly selected sample
UK Hypoglycaemia Study Group 2007 [74]	77[c]	70	Prospective multicentre study
	89[d]	10	
Akram et al. 2006 [124]	401	44	Retrospective clinic survey
Donnelly et al. 2005 [122]	173	35	Prospective study, population-based random sample
Henderson et al. 2003 [73]	215	28	Retrospective clinic survey, randomly selected sample
Murata et al. 2005 [125]	344	21	Prospective study, random Veterans Affairs sample
Saudek et al. 1996 [126]	62[e]	18	Clinical trial, multiple insulin injection group
Gürlek et al. 1999 [127]	114	15	Retrospective clinic survey
Abraira et al. 1995 [128]	75	3	Clinical trial, intensive insulin group
Yki-Järvinen et al. 1999 [129]	88	0	Clinical trial, initial insulin therapy
Ohkubo et al. 1995 [130]	52	0	Clinical trial, initial insulin therapy
Khunti et al. 2016 [123]	19563	250	Retrospective 6 mo and 4 wk self-reported prospective multinational survey in insulin-treated type 2 diabetes

[a] Insulin treatment for >15 yr.
[b] Insulin treatment for <5 yr.
[c] Insulin treatment for >5 yr.
[d] Definite (8 per 100 person-years) plus suspected (10 per 100 person-years).
[e] Insulin treatment for <2 yr.
Source: Adapted from Cryer et al. 2009 [131] by permission of the Endocrine Society.

of 10 and 70 episodes per 100 person-years, respectively. The pattern for self-treated hypoglycaemia was similar [74]. Thus, although the incidence of iatrogenic hypoglycaemia is relatively low (with current less than euglycemic goals) in the first few years of insulin treatment of type 2 diabetes, the risk increases substantially in advanced type 2 diabetes, approaching that in type 1 diabetes.

Because asymptomatic episodes will almost invariably be missed, and symptomatic episodes may not be recognized as the result of hypoglycaemia [66] and, even if they are, they are not long remembered [71, 137], estimates of the frequency of iatrogenic hypoglycaemia are underestimates. Although they represent only a small fraction of the total hypoglycaemic experience, because they are dramatic events that are more likely to be reported (by the person with diabetes or family or carers) [71, 137], estimates of the frequency of severe hypoglycaemia, requiring the assistance of another person, are more reliable, particularly if they are determined in population-based prospective studies focused on hypoglycaemia [1, 5].

The prospective population-based data of Donnelly et al. [122] indicate that the overall incidence of hypoglycaemia in insulin-treated type 2 diabetes is approximately one-third of that in type 1 diabetes (Table 40.3). The incidence of any and of severe hypoglycaemia was ~4300 and 115 episodes per 100 patient-years, respectively, in type 1 diabetes and ~1600 and 35 episodes per 100 patient-years, respectively, in insulin-treated type 2 diabetes. In addition, in population-based studies, the incidence of severe hypoglycaemia requiring emergency treatment in insulin-treated type 2 diabetes was ~40% [135] and ~100% [136] of that in type 1 diabetes. In the global Hypoglycaemia Awareness Tool study [123], using a six-month retrospective and four-week prospective self-adjustment questionnaire and diaries of 27 585 individuals with type 1 diabetes or insulin-treated type 2 diabetes worldwide, hypoglycaemia rates were three times higher than reported in population-based studies (Table 40.3). Because the prevalence of type 2 diabetes is ~20-fold greater than that of type 1 diabetes, and most people with type 2 diabetes ultimately require treatment with insulin, most episodes of iatrogenic hypoglycaemia, including severe hypoglycaemia, occur in people with type 2 diabetes.

Impact of hypoglycaemia

Iatrogenic hypoglycaemia causes recurrent physical and psychological morbidity, increases mortality, impairs defences against subsequent hypoglycaemia, and precludes maintenance of euglycaemia over a lifetime of diabetes [1, 5]. In the short term, it causes brain fuel deprivation that, if unchecked, results in functional brain failure that is typically corrected after the plasma glucose concentration is raised [3]. Rarely, it causes sudden, presumably cardiac arrhythmic [138, 139] death or, if it is profound and prolonged, brain death [3]. Three early reports indicated that 2–4% of people with diabetes die from hypoglycaemia [140–142]. More recent reports indicated that 6% [143], 7% [144], and 10% [145] of deaths of people with type 1 diabetes were the result of hypoglycaemia. In type 2 diabetes, mortality rates of up to 10% during episodes of severe sulfonylurea-induced hypoglycaemia have been reported [146]. In one trial of type 2 diabetes, between 1% and 9% of evaluable deaths were attributed to hypoglycaemia [147].

Excess mortality during intensive glycaemic therapy with increased rates of hypoglycaemia was found in randomized controlled trials (RCTs) in individuals in the intensive care unit [148] and in people with type 2 diabetes [119]. Overall, increased mortality has been consistently associated with severe hypoglycaemia in six RCTs, two in individuals in the intensive care unit [148, 149] and four in people with type 2 diabetes [119, 120, 150, 151].

The physical morbidity of an episode of hypoglycaemia ranges from unpleasant symptoms to seizure and coma [1, 3, 5]. It can impair judgement, behaviour, and performance of physical tasks. Permanent neurological damage is rare, although there is concern that recurrent hypoglycaemia might cause chronic cognitive impairment. The developing brain is susceptible to effects of severe hypoglycaemia [152, 153], while from young adulthood to middle age the brain may be more resistant [154]. Cumulative exposure to severe hypoglycaemia in early-onset type 1 diabetes may be associated with poorer cognitive performance in adulthood. In the 32-year follow-up of the DCCT trial, both higher HbA_{1c} and a larger number of severe hypoglycaemic episodes were associated with greater cognitive decline [155]. There was notably a dose–response relationship, with a higher number of severe hypoglycaemic episodes linked to greater decrements in psychomotor function and mental efficiency that was most evident in later life [155, 156]. The psychological morbidity of fear of hypoglycaemia [157] should not be underestimated and can pose a barrier to optimal glycaemic levels.

Hypoglycaemia and cardiovascular disease

Hypoglycaemia can lead to cardiovascular consequences [158]. The role of tight glycaemic management in reducing microvascular complications in newly diagnosed type 2 diabetes was established in the UK Prospective Diabetes Study (UKPDS) in 1998 [134]. While there was a non-significant reduction in the relative risk of myocardial infarction ($p = 0.052$) in the original trial, a 10-year follow-up of the UKPDS cohort showed significant reductions in myocardial infarction and cardiovascular mortality in the intensively treated group [159]. Three, multicentre RCTs subsequently tested the hypothesis that intensive glycaemic management reduces cardiovascular events in type 2 diabetes by recruiting 23 182 participants globally with known cardiovascular disease or established risk factors [117, 118, 150]. In all trials, no significant reduction in major cardiovascular events was observed. Indeed, mortality in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial actually increased [119]. Possible explanations for this include weight gain, specific medications, or simply the play of chance, but it is telling that compared to the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, where there was no increase in mortality, rates of severe hypoglycaemia in ACCORD were in the order of four to five times higher [158]. An association between hypoglycaemia and cardiovascular mortality has also been reported in type 1 diabetes, albeit less consistently [123, 160, 161]. It is uncertain, however, if the association between hypoglycaemia and cardiovascular mortality in diabetes is causal or due to confounding. Hypoglycaemia could be a marker for susceptibility by virtue of being more prevalent in those with comorbidities, including frailty, liver and kidney disease; these conditions are likely to lead to hypoglycaemia, but also independently increase the risk of cardiovascular mortality [162].

Concerns around confounding have led to additional *post hoc* analyses of global cohort studies (epidemiological and clinical trials) with tens and thousands of participants with type 1 diabetes and type 2 diabetes. Collectively, these studies demonstrate a 1.5–6-fold increased risk of cardiovascular events and mortality in those who experience hypoglycaemia compared with those who do not [158]. The association between hypoglycaemia and stroke,

however, is less convincing [163]. A large systematic review and meta-analysis of nearly a million people employed specific statistical adjustments to conclude that comorbidities alone cannot explain the relationship between hypoglycaemia and cardiovascular disease in type 2 diabetes [164]. Nonetheless, whether hypoglycaemia is a risk factor for cardiovascular disease or simply a risk marker is still debated [158]. A recent *post hoc* analysis of the DEVOTE trial population supports the hypothesis that hypoglycaemia is a risk factor for cardiovascular events in type 2 diabetes [165]. Further, Heller et al. recently conducted a *post hoc* analysis of the Liraglutide Effect and Action in Diabetes (LEADER) trial, first to test a potential association between non-severe and severe hypoglycaemia episodes; and second to test a potential association between hypoglycaemia severity and risk of subsequent cardiovascular events in those with type 2 diabetes [166]. Although non-severe hypoglycaemia episodes (>2 per year) were associated with an increased risk of severe hypoglycaemia, no association was found between lower rates (2–11 episodes per year) of non-severe hypoglycaemia and cardiovascular events; however, higher rates (≥12 episodes per year) of non-severe hypoglycaemia were associated with a higher risk of cardiovascular events and mortality, suggesting a dose–response relationship [166]. Overall, the true picture is likely to be multifactorial, with confounding and causality likely to be contributing and the magnitude of risk also influenced by the severity and frequency of hypoglycaemia, underlying cardiovascular risk, type and duration of diabetes, and potentially other as yet undetermined biological variables.

It is challenging to establish cause and effect between hypoglycaemia and cardiovascular events in diabetes through *post hoc* analyses. To definitively answer this question, a clinical trial would involve exposure of one group to severe hypoglycaemia while the other was not exposed, with cardiovascular events and mortality as key trial outcomes [158]. Such a study is impractical and clearly unethical, especially as intensive glycaemic management appears to confer a greater cardiovascular risk in those with a high pre-existing cardiovascular burden [167]. However, recent experimental studies have elucidated novel mechanisms through which hypoglycaemia could cause adverse cardiovascular events in those with diabetes [168–173]. These mechanisms are illustrated in Figure 40.9.

Clinical definition and classification of hypoglycaemia

The American Diabetes Association (ADA) and ADA/Endocrine Society Workgroups on Hypoglycaemia [174, 175] defined hypoglycaemia in diabetes as 'all episodes of abnormally low plasma glucose concentration that expose the individual to potential harm'. However, it is not possible to state a specific plasma glucose concentration that defines clinical hypoglycaemia; although symptoms typically develop at plasma glucose concentrations of 2.8–3.1 mmol/l (~50–55 mg/dl) (Figure 40.1) [176] in individuals without diabetes, the glycaemic threshold for symptoms (and also those for glucose counter-regulatory and cognitive dysfunction responses) shifts to lower plasma glucose concentrations in people with tightly managed diabetes and recurrent hypoglycaemia [59, 175], and to higher plasma glucose concentrations in those with suboptimally managed diabetes [59, 175, 177].

The ADA workgroups on hypoglycaemia with drug-treated diabetes (implicitly those treated with an insulin secretagogue or insulin) became concerned about the possibility of developing hypoglycaemia at a plasma glucose concentration of 3.9 mmol/l (≤70 mg/dl) [174, 175]. Within the error of self-monitoring of blood glucose (or continuous glucose sensing), that conservative alert value approximates the lower limit of the post-absorptive plasma glucose concentration range in people without diabetes [176] and the normal glycaemic thresholds for activation of physiological glucose counter-regulatory systems [176], and is low enough to reduce glycaemic defences against subsequent hypoglycaemia [61] in individuals without diabetes. Indeed, impairment of a complex function, driving, has been demonstrated at plasma glucose levels in this general range in type 1 diabetes [178]. It also generally provides some margin for the relative inaccuracy of glucose monitors at low plasma glucose concentrations.

The International Hypoglycaemia Study Group (IHSG) sought to standardize the definition of hypoglycaemia in clinical trials and proposed three levels of hypoglycaemia: level 1 (<3.9 mmol/l); level 2 (<3.0 mmol/l); and level 3, which corresponds to severe hypoglycaemia requiring external assistance (Table 40.4) [179]. The group recommended that glucose <3.0 mmol/l should be regarded as

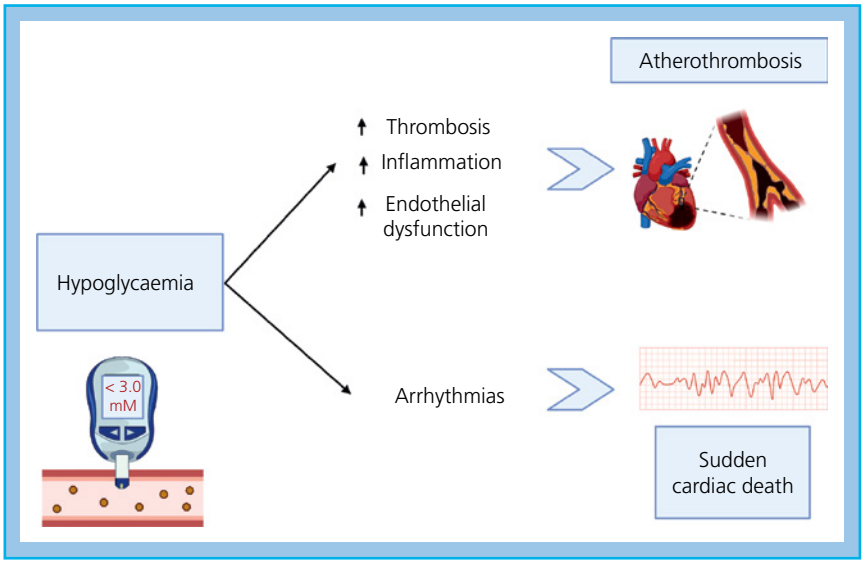

Figure 40.9 Mechanisms through which hypoglycaemia may cause adverse cardiovascular events. Source: Created by A. Iqbal in Biorender.com.

Table 40.4 International Hypoglycaemia Study Group definition of levels of hypoglycaemia that should be reported in clinical trials.

Level	Classification	Definition
1	Hypoglycaemia alert	Glucose <3.9 mmol/l (70 mg/dl)
2	Clinically important	Glucose <3.0 mmol/l (54 mg/dl) is sufficiently low to indicate serious, clinically important hypoglycaemia Should be reported in clinical trials
3	Severe	Severe hypoglycaemia with as defined by American Diabetes Association [175] denotes severe cognitive impairment requiring external assistance for recovery

Source: Modified by permission from International Hypoglycaemia Study Group 2017 [179].

clinically significant and should be reported in clinical trials. The basis for the proposed new classification is as follows:

- The level of 3 mmol/l (54 mg/dl) represented a glucose level below which clinically relevant consequences can develop; these include cognitive impairment, cardiac arrhythmias, and evidence that repeated episodes of glucose levels below this concentration can lead to impaired awareness and counter-regulatory impairment.
- Agreeing a third level (level 2) that was not severe but was clinically important would increase the statistical power of studies comparing different interventions to prevent and treat hypoglycaemia.
- Agreeing a revised classification would permit researchers to combine trial data in systematic reviews and permit meta-analysis.
- Adding the phrase 'cognitive impairment requiring the assistance of a third party' would allow paediatricians to adopt the same classification as used in adult practice. Paediatric classifications previously had defined severe hypoglycaemia as coma or needing parenteral therapy, as all young children 'need the help of another person' when treating any episode of hypoglycaemia.

The classification was adopted by both the ADA and the European Association for the Study of Diabetes (EASD) and subsequently by other organizations, including the Juvenile Diabetes Research Foundation (JDRF), International Society for Paediatric and Adolescent Diabetes (ISPAD), Advanced Technologies and Treatments for Diabetes (ATTD), and at least one regulator (European Medicines Agency, EMA).

Prevention and treatment of hypoglycaemia in diabetes: hypoglycaemia risk factor reduction

Iatrogenic hypoglycaemia is a barrier to glycaemic management in people with diabetes [1, 5], but the barrier can be lowered in individuals with diabetes by the practice of hypoglycaemia risk factor reduction (Table 40.5) [1, 5, 108]. That involves four steps:

1. Acknowledge the problem.
2. Apply the principles of aggressive glycaemic therapy [1, 5, 108, 180–184].
3. Consider the conventional risk factors for hypoglycaemia (Table 40.2).
4. Consider the risk factors for hypoglycaemia-associated counter-regulatory impairment in diabetes (Table 40.2).

Table 40.5 Hypoglycaemic risk factor reduction.

1. Acknowledge the problem
2. Apply the principles of aggressive glycaemic therapy
   - Diabetes self-management (patient education and empowerment)
   - Frequent self-monitoring of blood glucose and increasingly continuous glucose monitoring
   - Flexible and appropriate insulin (and other drug) regimens
   - Individualized glycaemic goals
   - Ongoing professional guidance and support
3. Consider the conventional risk factors for hypoglycaemia (Table 40.2)
4. Consider the risk factors indicative of hypoglycaemia-associated counter-regulatory impairment (Table 40.2)

The issue of hypoglycaemia should be addressed in every contact with people with diabetes, at least those treated with a sulfonylurea, a glinide, or insulin [1, 5, 108]. Acknowledging the problem allows the caregiver either to move on if hypoglycaemia is not an issue, or to address it, and keep it in perspective, if hypoglycaemia is an issue. Patient concerns about the reality, or even the possibility, of hypoglycaemia can be a barrier to glycaemic management [185, 186]. It is often helpful also to question close associates of the person with diabetes, because they may have observed clues to episodes of hypoglycaemia not recognized by the individual with diabetes. Even if no concerns are expressed, examination of the self-monitoring of blood glucose or CGM records will often disclose that hypoglycaemia is a problem.

If hypoglycaemia is an issue, the principles of intensive glycaemic therapy in diabetes [1, 5, 108, 180–184] should be reviewed and applied. These include diabetes self-management based on diabetes education and empowerment, frequent self-monitoring of blood glucose (and increasingly use of CGM), flexible and appropriate insulin (and other drug) regimens, individualized glycaemic goals, and ongoing professional guidance and support (Table 40.5).

Diabetes self-management education and empowerment are fundamentally important. As the therapeutic regimen becomes progressively more complex, both early in type 1 diabetes and later in type 2 diabetes, the success of glycaemic management becomes progressively more dependent on the many management decisions and skills of the well-informed person with diabetes. In addition to basic training about diabetes, people with insulin secretagogue or insulin-treated diabetes need to learn about hypoglycaemia [187]. They need to know the common symptoms of hypoglycaemia, and their individual most meaningful symptoms, and how to treat (and not overtreat) an episode. Close associates also need to be taught the symptoms and signs of hypoglycaemia, and when and how to administer glucagon. The individual needs to understand the relevant conventional risk factors for hypoglycaemia (Table 40.2), including the effects of the dose and timing of their individual secretagogue or insulin preparation(s) and also the effects of missed meals and the overnight fast, exercise, and alcohol ingestion. They also need to know that episodes of hypoglycaemia signal an increased likelihood of future, often more severe, hypoglycaemia [110, 111, 113, 115, 187–190]. Finally, individuals using an online glucose monitoring system need to apply those data critically to their attempts to minimize both hypoglycaemia and hyperglycaemia.

The core approach to virtually all individuals in whom iatrogenic hypoglycaemia becomes a problem is structured education (or often re-education), which reduces the rates of severe hypoglycaemia

[67, 191–193]. This is often coupled with short-term scrupulous avoidance of hypoglycaemia, which reverses impaired awareness of hypoglycaemia in most affected individuals [94–97]. The therapeutic objective is to minimize the number and the magnitude of episodes of hypoglycaemia, not to promote hyperglycaemia. Indeed, it is often possible to lower HbA_{1c}.

In people treated with an insulin secretagogue, and particularly those treated with insulin, frequent self-monitoring of blood glucose becomes progressively more key to diabetes self-management as the therapeutic regimen grows more complex, both early in type 1 diabetes and later in type 2 diabetes. Ideally, individuals should estimate their glucose levels whenever they suspect hypoglycaemia. That would not only confirm or exclude an episode of hypoglycaemia, it would also help the individual learn the key symptoms of their hypoglycaemic episodes and might lead to regimen adjustments. It is particularly important for people with impaired awareness of hypoglycaemia to monitor their glucose level before performing a critical task such as driving. Self-monitoring of blood glucose provides a glucose estimate only at one point in time; it does not indicate whether glucose levels are falling, stable, or rising. That limitation is addressed by evolving technologies for real-time CGM [194–196]. Subcutaneous glucose concentrations lag changes in plasma glucose by 10–15 minutes and their measurement suffers from some inaccuracy. Nonetheless, CGM is associated with an average HbA_{1c} reduction of 0.4–0.6% (4–6 mmol/mol) in adults with type 1 diabetes who used the device when prescribed without an increase in detected hypoglycaemia [194]. However, in one study, the sensitivity and specificity for the detection of low glucose levels were only 65% and 80%, respectively, and both false-negative and false-positive results were common [196].

Flexible and appropriate drug regimens are key components of hypoglycaemia risk factor reduction [1, 5, 108]. Hypoglycaemia is typically the result of relative or absolute therapeutic (endogenous or exogenous) insulin excess and compromised defences against falling plasma glucose concentrations. The relevant treatments include insulin or an insulin secretagogue such as a sulfonylurea (e.g. glibenclamide [glyburide], glipizide, glimepiride, and gliclazide) or a glinide (e.g. repaglinide and nateglinide). Early in the course of type 2 diabetes, people may respond to drugs that do not raise insulin levels at low or normal plasma glucose concentrations and therefore should not, and probably do not, cause hypoglycaemia [1, 5]. These include the biguanide metformin, which nonetheless has been reported to cause self-reported hypoglycaemia [115], thiazolidinediones, α-glucosidase inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, and sodium–glucose co-transporter 2 (SGLT-2) inhibitors. All these drugs require endogenous insulin secretion to lower plasma glucose concentrations, and insulin secretion declines appropriately as glucose levels fall into the normal range. That is true even for the GLP-1 receptor agonists and the DPP-4 inhibitors, which enhance glucose-stimulated insulin secretion (among other actions). They do not stimulate insulin secretion at normal or low plasma glucose concentrations (i.e. they increase insulin secretion in a glucose-dependent fashion). However, all five categories of drugs can increase the risk of hypoglycaemia if used with an insulin secretagogue or insulin.

Among the commonly used sulfonylureas, the longer-acting glibenclamide (glyburide) is more often associated with hypoglycaemia than the shorter-acting glimepiride [146, 197]. The use of long-acting insulin analogues (e.g. glargine or detemir), rather than neutral protamine Hagedorn (NPH) insulin, as the basal insulin in a multiple daily injection insulin regimen reduces at least the incidence of nocturnal hypoglycaemia, and perhaps also that of total, symptomatic, and nocturnal hypoglycaemia, in type 1 diabetes and type 2 diabetes [197–199]. The use of a rapid-acting analogue (e.g. lispro, aspart, or glulisine) as the prandial insulin in a multiple daily injection regimen reduces the incidence of nocturnal hypoglycaemia, at least in type 1 diabetes [198–201]. Second-generation basal analogues (insulin degludec, insulin glargine 300 U/ml) have more consistent pharmacokinetic profiles. Compared with first-generation insulin glargine 100 U/ml, both are associated with a lower risk of hypoglycaemia, particularly nocturnal hypoglycaemia, while achieving similar HbA_{1c} [202–204]. In a randomized crossover trial, insulin degludec was associated with lower rates of symptomatic hypoglycaemic episodes in people with type 1 diabetes (2201 vs 2463 episodes per 100 person-years' exposure) compared with insulin glargine 100 U/ml [205].

Significant advances have been made in CGM systems, which detect interstitial glucose using enzymatic sensors, integrated with a mobile reader to deliver real-time glucose levels (real-time or rtCGM) or on scanning (intermittently scanned or isCGM). Such systems can warn the user or care partner of hypoglycaemia or impending hypoglycaemia. In RCTs, rtCGM reduced hypoglycaemia compared with self-monitoring of blood glucose in type 1 diabetes [204], including those with impaired awareness [207]. In type 2 diabetes, use of isCGM reduced hypoglycaemia in open-label trial settings [208]. Significant reductions in severe hypoglycaemic events with isCGM were also reported in real-world settings [209], although the accuracy of CGM sensors in the hypoglycaemia range remains a limiting factor.

Because the basal insulin infusion rate can be varied across the day, continuous subcutaneous insulin infusion using insulin pumps should be superior to multiple daily injections. It may reduce HbA_{1c}, the frequency of hypoglycaemia, or both, in selected capable and motivated individuals [210]. However, in the HypoCOMPaSS trial [68], neither pump therapy alone (compared with multiple daily injections) nor CGM (compared with self-monitoring of blood glucose) reduced severe hypoglycaemia or improved awareness of hypoglycaemia to a greater extent. Sensor-augmented pumps, which combine rtCGM with an insulin pump, achieve an ~0.5% (5 mmol/mol) greater decrease in HbA_{1c} than multiple daily injections alone without an increase in hypoglycaemia [211, 212]. A sensor-augmented pump that temporarily suspends insulin infusion for up to two hours when the CGM value falls below a preselected level (a low glucose suspend [LGS] feature) reduces the frequency of severe hypoglycaemia [213, 214].

Significant advances have been made in closed-loop insulin delivery, which combines CGM and insulin pump with an automated controller. Current commercially available systems are hybrid closed-loop systems that provide algorithm-driven automated insulin delivery, but still require manual or *announced* mealtime boluses. Compared with sensor-augmented pumps, hybrid closed-loop systems have been associated with significant reductions in HbA_{1c} and time in hypoglycaemia by CGM in adults and adolescents with type 1 diabetes [215–216]. Bihormonal pumps, with automated delivery of both insulin and glucagon, are actively under clinical development and may confer additional protection from hypoglycaemia [219–221]. Islet transplantation can restore α- and β-cell function in longstanding type 1 diabetes in individuals with impaired awareness of hypoglycaemia or recurrent severe hypoglycaemia with undetectable C-peptide. Long-term follow-up of transplant recipients has shown that they remained completely

free of severe hypoglycaemic episodes at 10 years with reduced insulin requirements [222]. Although closed-loop and islet transplantation may be effective in reducing hypoglycaemia, the cost and complexity of these technologies currently preclude them from being used widely. Patient motivation and education remain paramount in achieving the best outcomes with new technologies. Indeed, several psycho-educational interventions, including blood glucose awareness training [223], have demonstrated reduced numbers of severe hypoglycaemia in recent trials.

Given the evidence that optimal glycaemic management partially prevents or delays microvascular complications of diabetes, and may partially prevent or delay macrovascular complications, it follows that a lower HbA_{1c} is in the best interests of people with diabetes if it can be achieved and maintained safely [138]. Thus, a reasonable individualized glycaemic goal is the lowest HbA_{1c} that does not cause severe hypoglycaemia, preferably with little or no symptomatic or even asymptomatic hypoglycaemia, at a given stage in the evolution of the individual's diabetes [138]. That links the selection of a glycaemic goal to the risk of hypoglycaemia, as well as the use of drugs that can cause hypoglycaemia and the type and duration of diabetes, a surrogate for endogenous insulin deficiency. If the therapeutic regimen produces severe hypoglycaemia or impaired awareness of hypoglycaemia, or an unacceptable number of symptomatic or asymptomatic episodes, hypoglycaemia has become a problem that needs to be addressed.

Because the glycaemic management of diabetes is empirical, caregivers should work with each individual over time to find the most effective and safest method of glycaemic management at a given point in the course of that person's diabetes. Care is best accomplished by a team that includes, in addition to a physician, professionals trained in, and dedicated to, translating the standards of care into the care of the individual and making full use of modern communication and computing technologies.

Another step is to consider the conventional risk factors for hypoglycaemia, especially those that result in both relative and absolute therapeutic insulin excess. In addition to insulin secretagogue or insulin doses, timing, and type, these include conditions in which exogenous glucose delivery or endogenous glucose production is decreased, glucose utilization or sensitivity to insulin is increased, or insulin clearance is reduced (Table 40.2).

Finally, the risk factors for counter-regulatory impairment need to be considered. These include the degree of endogenous insulin deficiency, a history of severe hypoglycaemia, impaired hypoglycaemia awareness, or both, and also any relationship between hypoglycaemic episodes and recent antecedent hypoglycaemia, prior exercise or sleep, and lower HbA_{1c} levels (Table 40.2). Unless the cause is easily remediable, a history of severe hypoglycaemia should prompt consideration of a fundamental regimen adjustment. Without that, the risk of a subsequent episode of severe hypoglycaemia is high [110, 111, 113, 115, 187–190]. Given a history of impaired awareness of hypoglycaemia, a 2–3-week period of scrupulous avoidance of hypoglycaemia, without running glucose levels high, is advisable since it may improve awareness [94–98]. Interestingly, few of the reversal studies have led to significant restoration of impaired counter-regulatory hormone responses [95–98]. A history of late post-exercise hypoglycaemia, nocturnal hypoglycaemia, or both should prompt appropriately timed regimen adjustments (generically, less insulin action, more carbohydrate ingestion, or both).

When prevention fails, treatment of hypoglycaemia becomes necessary. Most episodes of asymptomatic hypoglycaemia (detected by self-monitoring of blood glucose or CGM) and of mild–moderate symptomatic hypoglycaemia are effectively self-treated by ingestion of glucose tablets or carbohydrate-containing juice, soft drinks, other snacks, or a meal [224, 225]. A reasonable dose is 20 g of glucose [225]. Clinical improvement should occur in 15–20 minutes; however, in the setting of ongoing hyperinsulinaemia, the glycaemic response to oral glucose is transient, typically less than two hours [225]. Thus, ingestion of a more substantial snack or meal shortly after the plasma glucose concentration is raised is generally advisable.

Parenteral treatment is required when a hypoglycaemic patient is unwilling (because of neuroglycopaenia) or unable to take carbohydrate orally. Glucagon, injected subcutaneously or intramuscularly (in a usual dose of 1.0 mg in adults) by an associate of the patient, may be used. That can be life-saving, but it often causes substantial, albeit transient, hyperglycaemia and it can cause nausea or even vomiting. Smaller doses of glucagon (e.g. 150 μg), repeated if necessary, are effective without side effects [226]. Because it acts by stimulating hepatic glycogenolysis, glucagon is ineffective in glycogen-depleted individuals (e.g. following a binge of alcohol ingestion). New formulations of nasal glucagon are now available that are easier to administer. In a real-world prospective study, hypoglycaemic episodes resolved within 30 minutes of nasal glucagon administration, and in 95% of individuals and severe hypoglycaemic episodes resolved without additional external help within 15 minutes of receiving glucagon [227]. New glucagon analogues are also entering clinical practice as pre-filled pens with a long shelf-life.

Although glucagon can be administered intravenously by medical personnel, intravenous glucose is the standard parenteral therapy [224]. The glycaemic response to intravenous glucose is, of course, transient in the setting of ongoing hyperinsulinaemia.

The duration of an episode of iatrogenic hypoglycaemia is a function of its cause. An episode caused by a rapid-acting insulin secretagogue or insulin analogue will be relatively brief, while that caused by a long-acting sulfonylurea or insulin analogue will be substantially longer. The latter can result in prolonged hypoglycaemia requiring hospitalization for monitoring and parenteral glucose infusion if required.

Hypoglycaemia in children and adolescents

The majority of individuals with type 1 diabetes are adults, but nearly three-quarters of new type 1 diabetes diagnoses occur in childhood and adolescence [228]. Despite recent advances in knowledge, education, and diabetes technologies and treatments, most children and adolescents with type 1 diabetes do not achieve recommended glycaemic targets [229, 230]. Specifically, only a quarter of young people achieve the internationally established recommended HbA_{1c} target of <53 mmol/mmol (<7%), known to be associated with reduced diabetes complications in adulthood [231]. Hypoglycaemia and the fear of hypoglycaemia remain significant barriers to achieving these targets.

Hypoglycaemia is a common complication in the management of type 1 diabetes in children and adolescents. It interferes with daily living and poses a constant perceived threat to the individual and their families. It has long been recognized as a limiting factor in achieving optimal glycaemic levels [232] with an impact on quality of life [233]. As with adults, minimizing hypoglycaemia and its impact is a key objective of paediatric diabetes care.

Although hypoglycaemia in the young person with type 1 diabetes has much in common with hypoglycaemia in adults, there are important differences, which will be highlighted in this section. For example, there are differences in the physiology of the symptomatic and hormonal counter-regulatory responses to hypoglycaemia, its epidemiology, and risk factors. Furthermore, the impact of hypoglycaemia may differ because the child's organs, in particular the brain, are developing. In addition, the effects of changing behaviour as the young person matures modify the impact and response to hypoglycaemia. Finally, more so than for adults, the role and responses of caregivers are crucial.

Definition of hypoglycaemia in children and young people

The definition and classification of hypoglycaemia in children have been aligned with those in adults (Table 40.4) [234]. An important consideration in young children is that they require assistance to correct even mild hypoglycaemia. As a result, to define a severe event accurately requires an assessment by the caregiver and clinician as to the presence (or not) of hypoglycaemia-induced cognitive dysfunction. A subgroup of severe hypoglycaemia is hypoglycaemic coma: this is a hypoglycaemic event resulting in coma or convulsion. These events should be recorded independently, as they are unequivocal and significant in outcome.

The increasing adoption of CGM into routine clinical care, particularly in children [235], has added a new dimension to assessing hypoglycaemia. Using CGM, hypoglycaemia can be reported as a proportion of time spent with a sensor glucose value below a certain value. A recent international consensus recommended targets for sensor glucose: for time with sensor glucose <3.9 mmol/l (70 mg/dl) the target is <4% (1 h/d) and for time with sensor glucose <3.0 mmol/l (<54 mg/dl) the target is <1% (15 min) [236].

Prevalence and incidence of hypoglycaemia in children and young people

Mild hypoglycaemia is common and its exact incidence is difficult to determine. Unless CGM is used, asymptomatic hypoglycaemia and hypoglycaemia during sleep are unreported. Symptomatic hypoglycaemia occurs on an average twice per week. In contrast, the accurate recall of severe hypoglycaemia is more likely to be robust, although variations in definitions, sample sizes, and retrospective surveys have made comparisons between studies difficult.

The DCCT was one of the first studies to prospectively document hypoglycaemia incidence. In that trial there was a threefold increased risk of severe hypoglycaemia events in individuals randomized to the intensive management arm of the study and rates were higher in adolescents both in the intensive and conventional treatment arms [110]. The incidence of severe hypoglycaemia requiring treatment assistance was 61 per 100 person-years in those intensively treated. Similar high rates were reported in contemporary observational cohorts from Colorado and Western Australia [237, 238].

More recently, rates have substantially reduced. Population-based studies from Western Australia, Denmark, and Germany/Austria (Diabetes-Patienten-Verlaufsdokumentation, DPV registry) demonstrated a reduction of severe hypoglycaemia rates (convulsions and coma) in children and young people by >50% over the last two decades [238–241]. Historically, severe hypoglycaemia was associated with lower HbA_{1c} [242, 243], although this relationship has weakened in recent years, as observed in a large longitudinal cohort study from Europe and Australia, with a reduction in the rates of severe hypoglycaemia [244]. In that analysis, the severe hypoglycaemic coma rate decreased by an annual average of 2% and 6% in the European DPV and the Western Australian cohort, respectively. Likewise, younger age, historically a risk factor for severe events, did not increase the risk of severe hypoglycaemia, in spite of improved glycaemic levels [244, 245]. Similarly, a combined analysis from the US type 1 diabetes (T1D) Exchange and the DPV registry did not find increased rates of severe hypoglycaemic coma in those <6 years of age with HbA_{1c} <7.5% (58 mmol/mol) compared to those with higher HbA_{1c} [245]. The causes of these changes can only be subject to speculation, but improved knowledge and education along with increased use of insulin analogues and insulin pump therapy are likely contributors [240, 246–248]. Even though rates have reduced, hypoglycaemia continues to be a significant problem for young people living with diabetes and their families.

Signs and symptoms

As in adults, hypoglycaemia is often accompanied by signs and symptoms of autonomic (adrenergic) activation and/or neurological dysfunction from glucose deprivation in the brain (neuroglycopaenia). As the blood glucose falls, the initial symptoms result from activation of the autonomic nervous system and include shakiness, sweating, pallor, and palpitation. In healthy individuals with no diabetes, these symptoms occur at a higher blood glucose level in children than in adults (3.2–3.4 mmol/l [58–61 mg/dl] vs 2.8–3.1 mmol/l [50–56 mg/dl], children vs adults) [249]. The threshold for symptoms in individuals with diabetes will depend on their glycaemic levels [178, 249, 250], with an adaptive shift of the glycaemic threshold for symptom onset to a higher glucose level with chronic hyperglycaemia and a lower glucose level with chronic hypoglycaemia.

Signs of hypoglycaemia in children include behavioural changes: irritability, agitation, quietness, stubbornness, and tantrums may be the prominent symptom particularly for preschool children, and may result from a combination of neuroglycopaenic and autonomic responses [251]. In this younger age group, observed signs, such as pallor, are more important. The dominant symptoms of hypoglycaemia tend to differ depending on age, with neuroglycopaenia more common than autonomic symptoms in the young [252].

Physiological responses in children and adolescents

Although many of the physiological responses to hypoglycaemia are similar throughout the lifespan, developmental and age-related differences have been described in children and adolescents. As described for symptoms, counter-regulatory hormone responses differ in adolescents, who release catecholamines, cortisol, and growth hormone at a higher blood glucose than adults [249]. Adolescents also have deficient glucagon responses to hypoglycaemia within three months from diagnosis of type 1 diabetes [253].

To date, nearly all studies have been conducted in adolescents and young adults, primarily due to the difficulty of studying a younger age group. As a result, little is known about whether responses in pre-adolescents demonstrate a similar or different effect.

Impact and consequences of hypoglycaemia in children and young people

Hypoglycaemia is a constant concern for children, adolescents, and their families. Symptoms may be distressing or embarrassing, potentially compromising academic, social, and physical activities. Transient cognitive dysfunction associated with neuroglycopaenia can affect education and present a risk for the young person.

Furthermore, the daily requirement to adjust therapy to prevent hypoglycaemia is a significant ongoing burden for caregivers.

Psychological impact of hypoglycaemia
Severe hypoglycaemic episodes tend to have negative psychosocial consequences for the individual [254]. Fear of hypoglycaemia can induce anxiety and, although in some cases this anxiety can lead to appropriate vigilance in glucose management, high levels of anxiety can lead to disruptions in daily activities and suboptimal diabetes management [255]. Fear of hypoglycaemia can have impacts not only on the child but also the parents, and result in increased anxiety, poor sleep, and reduced quality of life [256]. This fear could lead families and/or physicians to accept high glucose levels, with behaviours directed towards avoiding hypoglycaemia leading to suboptimal glycaemic levels.

Neurological sequelae of hypoglycaemia
Although severe and prolonged hypoglycaemia has the potential to result in neurological impairment [257], multiple studies have only found subtle impacts of hypoglycaemia on the brain in children. Children with early-onset type 1 diabetes (<6 years of age) have cognitive defects on neuropsychological testing and changes on brain imaging [258]. This was assumed to be the result of hypoglycaemia, but detailed studies have not confirmed this and more recent evidence suggests that chronic hyperglycaemia [259,260] and even diabetic ketoacidosis [261] are more injurious to the brain in the young.

Impaired awareness of hypoglycaemia
Impaired awareness of hypoglycaemia may develop in children as well as adults, with a prevalence of between 19% and 37% [262,263]. As in adults, impaired awareness is associated with a significantly increased risk of a severe hypoglycaemia event [262]. Determining the level of hypoglycaemia awareness is an important component of routine clinical care.

Mortality
Mortality from hypoglycaemia in children and young people is rare, but has been reported [144,145]. Although rare, it is a common source of parental anxiety and fear of hypoglycaemia.

Risk factors for hypoglycaemia in children and young people

Undoubtedly, the most important risk factor for hypoglycaemia lies within insulin therapy itself and the mismatch between administered insulin and consumed food. An absolute excess of insulin could result from increased doses due to poor understanding of insulin type and action or accidental delivery. Similarly, a relative insulin excess is seen with reduced food intake or missed meals, and in situations where glucose utilization is increased (during exercise) or endogenous glucose production is decreased (after alcohol intake).

Managing type 1 diabetes and balancing the risk factors for hypoglycaemia in young children and young people present unique challenges owing to the child's developmental level, unpredictability of an infant or toddler's dietary intake, and the child's irregular activity level, emotional maturity, and behaviour.

Risk factors for recurrent hypoglycaemia
Most children with type 1 diabetes who experience severe hypoglycaemia have isolated events; however, a few experience recurrent episodes. After a severe episode, the risk of recurrent severe events is increased, in one report for up to four years [264]. When hypoglycaemia is recurrent, it is important to exclude impaired awareness of hypoglycaemia and rule out coexisting autoimmune disorders, such as subclinical hypothyroidism, coeliac disease, and Addison' disease [265–267]. Unexplained hypoglycaemia particularly in adolescence may be factitious due to self-administration, often a sign of psychological distress [268].

Exercise
Glucose response to exercise is affected by many factors, including the duration, intensity, and type of exercise; the time of day when exercise is performed; plasma glucose and insulin levels; and the availability of supplemental and stored carbohydrates [269,270]. The risk of hypoglycaemia is increased immediately after or during exercise, but may also be delayed up to 12 hours after exercise due to changes in insulin sensitivity and muscle glycogen restoration [271]. A range of strategies may be used to prevent exercise-induced hypoglycaemia, including close glucose monitoring, altering insulin doses, and carbohydrate ingestion [269].

Alcohol
Alcohol inhibits gluconeogenesis and may lead to hypoglycaemia [272]. Furthermore, the symptoms of hypoglycaemia may be obscured or masked by the cerebral effects of alcohol.

Nocturnal hypoglycaemia
Hypoglycaemia during sleep is a major concern for parents, and children have more frequent and prolonged periods of hypoglycaemia at night [273]. Younger age, lower HbA_{1c}, antecedent exercise, and hypoglycaemia are associated with a greater frequency of nocturnal hypoglycaemia [274]. Counter-regulatory catecholamine responses to hypoglycaemia are suppressed during sleep.

Hypoglycaemia treatment in children and young people

A goal of diabetes education is the prevention of hypoglycaemia through awareness of the problem, recognition of risk factors, regular glucose monitoring, and self-care behaviours such as appropriate insulin dosing and food intake. Despite this, hypoglycaemia may occur and a treatment plan is a required component of management.

When the glucose level falls below 3.9 mmol/l (70 mg/dl), remedial actions to prevent a further drop in glucose are recommended. The amount of glucose required may vary between individuals, circumstances, and insulin treatment. One study found that in children, 0.3 g/kg of rapidly acting carbohydrate-containing preparations effectively resolves hypoglycaemia in most children and raises median blood glucose by 1–1.3 mmol/l (90–113 mg/dl) in 10 minutes and 2.0–2.1 mmol/l (180–190 mg/dl) in 15 minutes without rebound hyperglycaemia at the next meal [275]. For children using insulin pump therapy, a lower amount of glucose may be required along with suspension of insulin delivery [276].

Urgent treatment is required in the event of severe hypoglycaemia, which can be safely reversed by glucagon administered intravenously, intranasally, intramuscularly, or subcutaneously [277,278]. In hospital, intravenous glucose or glucagon may be given. Intravenous glucose should be administered by trained personnel over several minutes to reverse hypoglycaemia. If glucose is given in excessive concentration (50% dextrose) or too rapidly, there is a risk of brain injury due to rapid osmolar change and cerebral oedema [279].

Diabetes technology and hypoglycaemia in children and young people

The introduction of diabetes technologies into routine diabetes care has offered new approaches to reducing the impact of hypoglycaemia on young people with type 1 diabetes. Insulin pump therapy has been associated with lower hypoglycaemia rates in trials and real-world data reports [280, 281]. With pump therapy it is possible to adjust insulin delivery to more closely mimic physiological insulin delivery. CGM provides 24-hour glucose monitoring and allows the individual, or healthcare providers, to assess trends in glucose levels and early intervention to prevent hypoglycaemia. Trials and real-world outcome studies have shown reduced rates of hypoglycaemia with the use of these systems [281–283]. CGM that has the capacity for remote monitoring has the potential to provide caregivers with an alarm if glucose levels in a child are falling; in one trial their use was associated with improved parental quality of life and better sleep [284].

Sensor-augmented pump therapy with insulin suspension

The incorporation of algorithms that automatically suspend insulin delivery based on sensor glucose readings reduces the incidence of severe hypoglycaemia and the time spent in a low glucose range [214, 285, 286]. Current systems suspend on predicted hypoglycaemia.

Automated insulin delivery systems (hybrid closed-loop)

Automated insulin delivery, with continuous glucose sensing and insulin delivery without user intervention, offers the potential to reduce the significant glycaemic excursions associated with conventional therapy. These systems utilize a control algorithm that autonomously and continually increases and decreases the subcutaneous delivery of insulin on the basis of real-time sensor glucose levels. These devices improve the time in target glucose range and reduce the time spent in hypoglycaemia in clinical trials and observational studies [215, 287–289].

Perspective on hypoglycaemia in diabetes

Glycaemic management, a focus of this chapter, is but one aspect of the management of diabetes. It is now possible to drive plasma low-density lipoprotein (LDL) cholesterol concentrations to subphysiological levels and to normalize blood pressure pharmacologically, usually without major side effects, in most people with diabetes. Weight loss and smoking cessation are more challenging. Although it is not possible to maintain euglycaemia over a lifetime of diabetes, because of the barrier of hypoglycaemia, maintenance of the lowest mean glycaemia that can be accomplished safely is in the best interests of people with diabetes.

Despite the difficulty, people with diabetes and their caregivers should keep the problem of iatrogenic hypoglycaemia in perspective. Early in the course of type 2 diabetes, by far the most common type of diabetes, hyperglycaemia may respond to lifestyle changes, specifically weight loss, or to anti-diabetes drugs that do not raise insulin levels and therefore do not cause hypoglycaemia. In theory, when such drugs are effective in the absence of side effects, there is no reason not to accelerate their dosing until euglycaemia is achieved. Over time, however, as people with type 2 diabetes become progressively more insulin deficient, those drugs, even in combination, fail to maintain glycaemic levels. Insulin secretagogues are also effective early in the course of type 2 diabetes, but they cause hyperinsulinaemia and therefore introduce both the risk of weight gain and hypoglycaemia. Euglycaemia is not an appropriate goal during therapy with an insulin secretagogue or with insulin. Nonetheless, the frequency of hypoglycaemia is relatively low during treatment with an insulin secretagogue or even with insulin early in the course of type 2 diabetes when glycaemic defences against falling plasma glucose concentrations are still intact. Therefore, over much of the course of the most common type of diabetes, it is possible to maintain a meaningful glycaemic level with a relatively low risk of hypoglycaemia.

The challenge is greater in people with advanced type 2 diabetes and type 1 diabetes caused by compromised defences against falling plasma glucose concentrations and the resulting higher barrier of iatrogenic hypoglycaemia. It is striking that it is 30 years since the recognition of the importance of repeated episodes of antecedent hypoglycaemia in damaging counter-regulatory mechanisms leading to impaired awareness of hypoglycaemia. Yet despite a substantial research effort in both basic and clinical arenas, our only effective therapeutic approaches involve therapeutic interventions that reduce the time individuals spend in hypoglycaemia. Nonetheless, concerns about hypoglycaemia should not be used as an excuse for suboptimal glycaemic levels. It should be recalled that the DCCT [110, 290] documented that the relationship between microvascular complications and mean glycaemia is curvilinear: some degree of glycaemic management puts the person with diabetes at substantially lower risk than little or no glycaemic management.

Diabetes will eventually be cured and prevented. Pending that, elimination of hypoglycaemia from the lives of people with diabetes will probably be accomplished by new treatment methods that provide plasma glucose–regulated insulin replacement or secretion. In the meantime, innovative research is needed if we are to improve the lives of all people affected by diabetes by lowering the barrier of iatrogenic hypoglycaemia.

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41 Acute Metabolic Complications of Diabetes: Diabetic Ketoacidosis and the Hyperosmolar Hyperglycaemic State in Adults

Philip Newland-Jones[1], Mayank Patel[1], and Ketan Dhatariya[2]

[1] University Hospital Southampton NHS Foundation Trust, Southampton, UK

[2] Norfolk and Norwich University Hospitals NHS Foundation Trust and University of East Anglia, Norwich, UK

Key points

Diabetic ketoacidosis:

- Diabetic ketoacidosis (DKA) is based on a triad of hyperglycaemia, ketonaemia, and metabolic acidosis with a high anion gap.
- The most common causes are infection or insulin omission or inadequate dosing.
- Nausea, vomiting, abdominal pain, and Kussmaul breathing are key features, along with osmotic diuresis due to hyperglycaemia and ketonaemia.
- Administration of intravenous fluid and insulin aims to correct dehydration, hyperglycaemia, and electrolyte imbalances.
- Identification of underlying causes and precipitants will reduce the risk of recurrence.

Hyperosmolar hyperglycaemic state:

- Hyperosmolar hyperglycaemic state (HHS) is characterized by hyperosmolarity due to extreme hypovolaemia, hyperglycaemia, and electrolyte disturbance.
- It typically affects older individuals with type 2 diabetes or reveals newly diagnosed type 2 diabetes in a much wider age range.
- The most common cause is infection, although other acute situations that release counter-regulatory stress hormones such as surgery, trauma, acute coronary syndromes, or acute stroke can also predispose to HHS.
- Fluid resuscitation and electrolyte management form the mainstay of treatment, with many individuals also requiring intravenous insulin.

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) are life-threatening emergencies in diabetes. Prompt clinical suspicion is vitally important to ensure early diagnosis, thus enabling protocol-based treatment to be commenced promptly, to reduce morbidity and mortality. Though discussed as clinically distinct phenomena, DKA and HHS should be considered as different points on the spectrum of hyperglycaemic emergencies. Both are characterized by hyperglycaemia with insulinopaenia, with only the degree of hyperglycaemia, level of associated dehydration, and severity of the associated metabolic acidosis distinguishing them [1–4]. Hospital-based treatment involves close monitoring, careful fluid replacement to restore circulation, and correction of electrolyte derangement and hyperglycaemia, with effort made to identify the precipitant so that future preventive measures can be taken. This chapter reviews the pathogenesis and pathophysiology, precipitating factors, clinical presentation, management, complications, and prevention of DKA and HHS.

Diabetic ketoacidosis

Definitions

Diabetic ketoacidosis (DKA) is based on a triad of hyperglycaemia (blood glucose >11 mmol/l (200 mg/dL) or known diabetes), ketonaemia (>3 mmol/l; 30 mg/dL), and a metabolic acidosis with a high anion gap (serum bicarbonate <15 mmol/l and/or venous pH <7.3) (Table 41.1) [4,6]. DKA is the result of either absolute or relative insulin deficiency in the context of increased counter-regulatory hormones that increase insulin resistance and reduce insulin secretion [4,7]. DKA occurs much more commonly in those with type 1 diabetes and was considered to be one of the key clinical features that differentiated type 1 diabetes; however, it can also occur in those with type 2 diabetes during intercurrent illness or surgical stress, and more rarely in newly diagnosed type 2 diabetes [8,9]. This ketosis-prone type 2 diabetes seems to present more commonly in those of African or Hispanic origin,

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Table 41.1 Diagnostic criteria for diabetic ketoacidosis.

Diabetic ketoacidosis – All 3 of the following:

- Plasma glucose concentration >11.1 mmol/l (200 mg/dL) or a previous history of diabetes mellitus
- Plasma ketones of ≥3 mmol/l or 30 mg/dL (urine ketones can be misleading and unhelpful)
- pH <7.30, anion gap >12, or bicarbonate <15 mmol/l

	Severity		
	Mild	**Moderate**	**Severe**
Arterial or venous pH	7.25–7.30	7.0–7.24	<7.0
Bicarbonate (mmol/l)	15–18	10–14.9	<10
Anion gap	10–12	>12	>12
Mental status	Alert	Alert/drowsy	Stupor/coma

Source: Adapted from Dhatariya et al. 2020 [5] (criteria) and Kitabchi et al. 2009 [3] (severity).

although it can occur in all populations. Despite presenting with DKA with insulin insufficiency, people with type 2 diabetes will often restore and recover β-cell function quickly after treatment, thus avoiding the need for ongoing insulin therapy [8]. With increasing use of sodium–glucose cotransporter 2 (SGLT-2) inhibitors in the treatment of type 2 diabetes, there is a growing number of individuals developing euglycaemic DKA (blood glucose 4–11 mmol/l; 70–200 mg/dL), a potential complication of this class of medication. It is more common in those using concomitant insulin therapy and the risk is significantly increased if medication cessation *sick-day rule* advice is not followed during intercurrent illness or surgical stress (ensuring that the individual knows never to stop basal insulin in type 1 diabetes, keeps well hydrated, monitors glucose and ketone levels every 2–3 hours, taking additional insulin if indicated, and seeks advice promptly when unwell) [10–12]. Overall, mortality with DKA has been reported as less than 1%, but a recent review of mortality in the UK reported that between 2017 and 2019 the mortality rate was 3.8% [13]. This increases considerably with ageing, which is likely related to the underlying precipitant of the DKA (e.g. infection, trauma), with mortality rates for those over 65 years old reaching 10–20% [3,14].

Pathogenesis and pathophysiology

Although the mechanisms for the development of DKA are multifactorial, there is always an undercurrent of absolute or relative insulin deficiency, often with a concomitant increase in counter-regulatory hormones (glucagon, catecholamines, cortisol, and growth hormone) [4,7,15]. This mismatch in insulin production and insulin requirement leads to hydrolysis of triglycerides, delivering free fatty acids to the liver, which leads to the production of ketones (β-hydroxybutyrate, acetoacetate, and acetone) [4,7,15]. Counter-regulatory hormones increase gluconeogenesis and glycogenolysis, resulting in hyperglycaemia worsening osmotic diuresis, leading to hypovolaemia and higher concentrations of ketone bodies and glucose, leading to a metabolic acidosis [4,16,17]. Figure 41.1 outlines the pathogenesis of DKA.

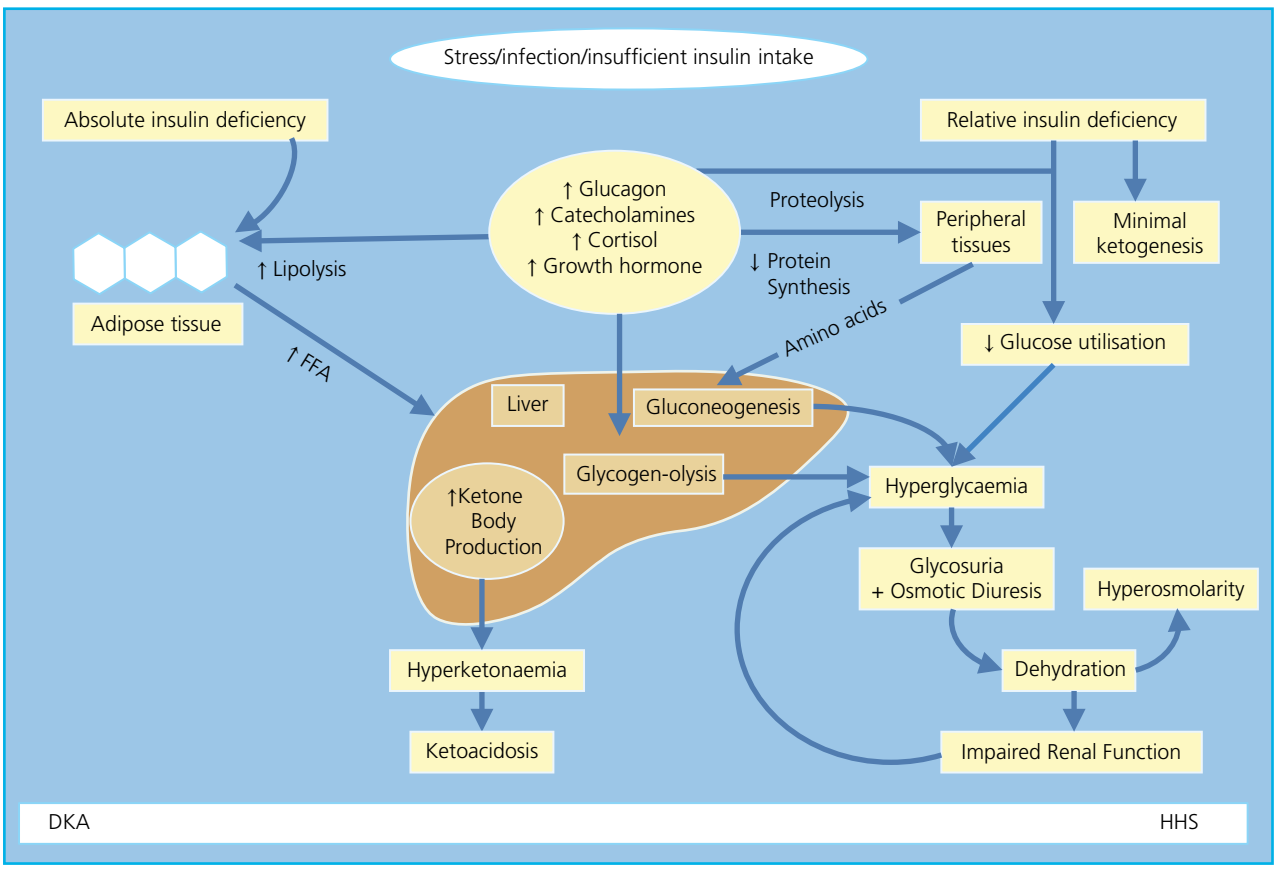

Figure 41.1 Pathogenesis of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS). FFA, free fatty acids. Source: Reproduced from English and Williams 2004 [15] by permission of BMJ Publishing Group Ltd.

Hyperglycaemia

Hyperglycaemia in DKA is predominantly caused by the cumulative effect of absolute or relative insulin deficiency in the context of raised counter-regulatory hormones. This results in increased gluconeogenesis, glycogenolysis, and an impairment in peripheral glucose utilization, leading to hyperglycaemia [16, 18]. Both hypercortisolaemia and insulin deficiency lead to catabolism of protein from muscles, providing amino acid precursors for gluconeogenesis and ketogenesis [19–21]. The severity of hyperglycaemia is further exacerbated by osmotic diuresis driven by increased glucose levels. This osmotic diuresis leads to dehydration, hypovolaemia, and a reduction in glomerular filtration rate, which will further concentrate glucose and reduce glucose excretion [22].

Ketogenesis and ketoacidosis

Insulin deficiency and an increase in counter-regulatory hormones lead to the release of free fatty acids and glycerol from adipose tissue through increased tissue lipase activity, which in turn leads to unrestricted oxidation in the liver and ketone generation [23–25]. Acetone, acetoacetate, and β-hydroxybutyrate form the three ketone bodies generated by the liver. Acetone gives the classic *fruity* or *pear-drops* breath in those in DKA. The remaining acidic ketone bodies, acetoacetate and β-hydroxybutyrate, accumulate, leading to a decrease in serum bicarbonate concentration, the development of a high anion gap, and metabolic acidosis [26–29]. The severity of DKA is differentiated by the degree of acidosis and associated mental status, where acidosis, if severe and prolonged, can lead to irreversible damage, coma, and death.

Fluid and electrolyte disturbance

Both hyperglycaemia and ketonaemia precipitate an osmotic diuresis that leads to dehydration, hypovolaemia, and loss of electrolytes [22]. Hypovolaemia decreases glomerular filtration rate and increases counter-regulatory hormones further, which exacerbates existing hyperglycaemia and may also cause hypoperfusion, resulting in increased lactic acid levels [4, 7, 22]. The combination of osmotic diuresis, vomiting due to ketosis, and subsequent inability to maintain fluid intake can lead to severe dehydration, which makes avoidance of hospitalization difficult. A combination of acidosis, insulin deficiency, and hypertonicity cause a shift of potassium from the intracellular to the extracellular space, where it may be excreted in the urine or lost in vomit [15]. Hypovolaemia increases the concentration of aldosterone, which through promotion of sodium reabsorption in the kidneys leads to the excretion of potassium in the urine, further exacerbating potassium loss. This often results in an acute presentation of hyperkalaemia on a background of an overall total body deficit in potassium stores, which becomes evident on treatment initiation with fluid and insulin [22, 30]. Phosphate and magnesium are also often depleted on presentation of DKA, with the effects possibly exacerbating the arrhythmogenic effect of hyper- or hypokalaemia described [7].

Sodium–glucose cotransporter 2 inhibitor–induced ketoacidosis

The use of SGLT-2 inhibitors has increased significantly in recent years, leading to an increase in presentation of euglycaemic DKA [31]. It is usually precipitated by intercurrent illness or metabolic stress (surgery, infection, decreased oral intake, gastrointestinal losses), where appropriate medication cessation has not occurred as described in sick-day rule guidance [32]. SGLT-2 inhibitors create a pseudo-fasted state, the promotion of glycosuria, and lower circulating glucose levels, to which the body responds by reducing insulin production and increasing glucagon release. During intercurrent illness and subsequent increased insulin resistance due to counter-regulatory hormones, a disconnect between insulin requirement and production develops. The relative insulinopaenia leads to increased lipolysis, ketosis, and eventually acidosis, but importantly, due to ongoing glycosuria and low plasma glucose, this occurs in the context of euglycaemia rather than hyperglycaemia [32–34].

Precipitating factors

Initial presentation with DKA at the point of diagnosis of type 1 diabetes is more common in children, but can occur in up to 20% of adults with diabetes [35, 36]. For those with known diabetes, the most common precipitants are infections, intercurrent illness, and insulin omission or inadequate dosing (Table 41.2). A large single-centre study of 786 consecutive admissions showed that the distribution of precipitants has changed over time, with intercurrent illness and suboptimal insulin dosing remaining the most common causes, but increasingly SGLT-2 inhibitor use, immune therapy–induced diabetes [38], and Covid-19 infection also being causes [39].

The importance of the relationship between psychological factors and insulin treatment should not be underplayed. Diabetes distress, depression, anxiety, and eating disorders are common among people with type 1 diabetes, which can increase the risk of developing DKA [35, 40–42]. During the initial stages of the Covid-19 pandemic, national data from across England showed that admissions for DKA in those known to have type 1 diabetes dropped significantly [43]. It was thought that this was due to being in lockdown: people were able to pay more attention to their diabetes, but were also following their sick-day rules. However, the same data showed that admissions with DKA in those with known type 2

Table 41.2 Potential causes of diabetic ketoacidosis.

Intercurrent illness
Infection
Surgical stress
Trauma
Myocardial infarction
Cerebrovascular accident
Inadequate insulin dosing or omission
Sepsis
New presentation of type 1 diabetes
Alcohol excess
Mechanical factors
Broken insulin pen
Problems with insulin infusion pump
Problems with insulin administration technique
Expired insulin
Human factors
Insulin erroneously withheld in hospital
Pharmacological
Sodium–glucose cotransporter 2 (SGLT-2) inhibitor therapy
Corticosteroids
Thiazides
Pentamidine
Immune checkpoint inhibitors
Second generation (atypical) antipsychotics
Pregnancy

Source: Adapted from Patel 2021 [37] and Akturk et al. [38].

diabetes rose significantly, as well as in those newly diagnosed with diabetes [43]. Again, it was thought that there was a behavioural aspect to this, with people not seeking help from primary or secondary care teams (or unable to do so), and thus when they did present they were sicker than they otherwise might have been had they had swifter access to healthcare professionals. To prevent DKA recurrence, it is important to clearly identify the underlying cause for DKA and formulate a plan via a shared decision-making process.

Clinical presentation and diagnosis

Though often preceded by a brief period of general malaise, DKA usually develops in less than 24 hours and can affect both young and old individuals, so age at presentation is less relevant. Common presenting symptoms with their associated underlying pathophysiological causes and signs are shown in Table 41.3. Nausea, vomiting, and abdominal pain are relatively common early features, most likely due to a combination of evolving ketonaemia, dehydration, and delayed gastric emptying [35, 44]. Physical examination often reveals signs of dehydration, such as reduced skin turgor, hypotension, and tachycardia. Impaired mental state, drowsiness, and coma can also result. In particular, clinicians must be aware that rapid, deep breathing (Kussmaul respiration) may not just reflect a primary respiratory problem, but actually represent an appropriate physiological response to the significant metabolic acidosis in DKA [35, 45]. Fever often suggests a concurrent infection.

The diagnosis of DKA is made based on the presence of all three of hyperglycaemia, ketonaemia, and metabolic acidosis (Table 41.1) [3, 46]. It can be classified as mild, moderate, or severe, based on the degree of acidosis and conscious level [3]. There are plans to publish update diagnostic criteria in late 2023, unifying the most commonly used definitions from the UK and the USA [3, 27]. Ketoacidosis has also been reported with normal to modestly elevated glucose levels, particularly in association with pregnancy, prolonged starvation, and use of SGLT-2 inhibitors [10, 47, 48]. Reduced hepatic glucose output, with an associated low blood glucose concentration, can also be associated with alcohol dependency and significant liver disease [4, 49, 50].

Table 41.3 Clinical features of diabetic ketoacidosis.

Symptoms	Signs
Unplanned weight loss (Adipose and muscle breakdown-usually *new* type 1 diabetes) Polyuria, polydipsia (Osmotic diuresis due to hyperglycaemia) Blurred vision (Change in water content in eyeball and lens Nausea and vomiting) (Hyperketonaemia) Abdominal pain (Acidosis-induced ileus) Lethargy (Cells lacking glucose as metabolic substrate) Shortness of breath (Increased work of breathing to correct acidotic state by expelling carbon dioxide)	Ketonuria Glycosuria Fruity smell on breath (acetone) Tachypnoea Kussmaul breathing – deep and laboured Dehydration ± postural drop in blood pressure Tachycardia

Source: Adapted from Dhatariya et al. 2020 [4] and Patel 2021 [37].

Measurement of blood β-hydroxybutyrate rather than urinary acetoacetate ketone is preferred, as this provides a real-time quantitative indicator of the key metabolic product in DKA, which can be monitored serially when treatment is commenced as one of the markers of metabolic recovery [27, 28, 51]. Blood gas analysis is also essential, to inform the degree and confirm the expected raised anion gap metabolic acidosis state ($([Na^+] + [K^+]) - ([Cl^-] + [HCO3^-])$), with consideration given to the other causes of a raised anion gap that could be clinically relevant (e.g. salicylate poisoning). Development of a transient hyperchloraemic non-anion gap metabolic acidosis during treatment is also commonly observed and, although it has no acute adverse effects, may slow down time to DKA resolution [7, 51, 52]. Baseline biochemical electrolyte and haematological profiles should be measured too, along with hepatic and renal function. Other investigations, such as blood cultures, myocardial biomarkers, and a chest X-ray, should be performed if clinically indicated, with an electrocardiogram also useful to identify any potassium-related cardiac rhythm disturbances [37].

Serum potassium is usually elevated at presentation in DKA [4, 7]. This is a result of insulin deficiency, acidaemia, and water deficiency, promoting an intracellular to extracellular shift of potassium [22, 30]. The serum sodium level is typically low as a result of the osmotic shift of water from the intracellular to the extracellular space when hyperglycaemia is present. Though leucocytosis is a common finding, it often does not suggest active infection [53]. The presence of nausea, vomiting, and abdominal pain should also prompt a measurement of serum amylase, to exclude acute pancreatitis, though hyperamylasaemia is not definitive for a diagnosis of pancreatitis in DKA [44].

Management

The management of DKA is based on four key goals [4]:

- To restore circulating volume.
- To correct hyperglycaemia through the parallel reduction of serum glucose and plasma osmolarity.
- To correct hyperketonaemia and electrolyte imbalance.
- To identify and address precipitating factors.

Close monitoring is essential, with strict fluid balance and careful use of insulin other key elements of management. Serial monitoring of glucose, electrolytes, venous pH, bicarbonate, and β-hydroxybutyrate can also help track metabolic progress towards DKA resolution. Those with severe DKA or with an underlying critical illness should be managed in the intensive care unit (ICU), while mild to moderate DKA cases can be managed in an appropriate acute (level 1 care) general ward [3, 54–57]. Management is usually protocol driven, with consideration given to the aforementioned key goals. An example is given in Figure 41.2.

Fluid therapy

Given that there is an estimated fluid deficit of 100 ml/kg body weight at diagnosis, aggressive fluid replacement is a key early priority, to expand intravascular volume and restore renal perfusion [7]. In addition, fluid replacement is useful for improving insulin sensitivity by reducing circulating counter-regulatory hormones and diluting plasma glucose levels. The aim is to replace half of the estimated fluid deficit over 24 hours [3, 27]. The UK guidelines state that 0.9% sodium chloride infused at 500–1000 ml/h for the first 1–2 h will usually restore blood pressure and renal perfusion. The rate and choice of subsequent fluids used will depend on the haemodynamic and hydration state, as well as serum electrolyte levels and urine output [3, 27]. For the majority of individuals,

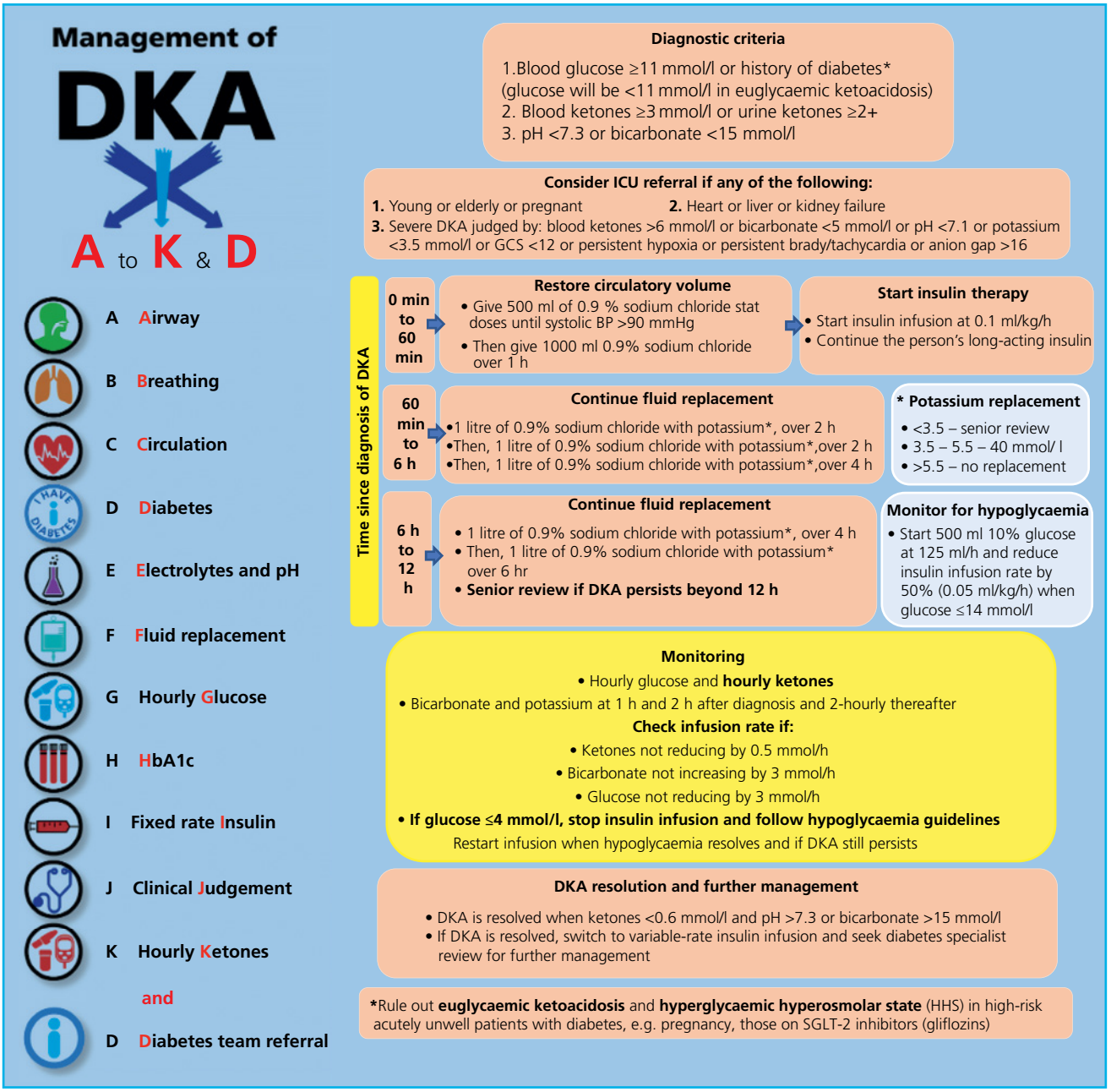

Figure 41.2 Management of diabetic ketoacidosis (DKA). BP, blood pressure; GCS, Glasgow coma score; HbA_{1c}, glycated haemoglobin; ICU, intensive care unit; SGLT-2, sodium–glucose cotransporter 2. Source: Adapted by permission from Kempegowda et al. 2019 [58].

continuation with 0.9% sodium chloride is appropriate at 250–500 ml/h, reducing stepwise as hydration improves. If the serum sodium is elevated, then a reduction of infusion rate to 166–250 ml/h would be suggested, or a switch to 0.45% sodium chloride infused at 250–500 ml/h [3, 27, 46].

Resolution of hyperglycaemia will often occur far quicker than resolution of ketonaemia, therefore to ensure continued adequate insulin administration for DKA resolution, plasma glucose levels should be maintained in a safe range by the addition of glucose infusion fluids. Intravenous 5–10% glucose should be infused additionally when the plasma glucose is approximately 14 mmol/l (250 mg/dL), enabling continued insulin administration until ketonaemia is reduced, while lowering the risk of hypoglycaemia [27].

Insulin therapy

Insulin administration is an essential element of DKA management, as it both increases peripheral glucose utilization and decreases hepatic glucose output. Moreover, it inhibits the release of free fatty acid from adipose tissue and decreases ketogenesis. A common effective practice is to administer an initial intravenous or intramuscular bolus of rapid-acting insulin (0.1 units/kg of body weight), followed by a continuous fixed-rate intravenous insulin infusion of soluble (regular) insulin (0.1 units/kg/h), although there is sufficient evidence to suggest that the initial bolus is not required if there is prompt intravenous access and treatment initiation with a continuous infusion [3, 27, 59]. For DKA associated with Covid-19 infection, it has been reported

that individuals are highly insulin resistant, requiring much higher doses [60]. The reasons for this remain unknown, and the addition of dexamethasone to aid in recovery will increase insulin resistance further.

The UK and American guidelines are now aligned with regard to fixed-rate insulin adjustment when glucose has dropped to <14 mmol/l (250 mg/dL), with the updated guidance advising reduction of the insulin infusion rate to 0.05 units/kg/h, alongside initiation of glucose-containing fluids to avoid hypoglycaemia during DKA treatment in response to a national survey of practice [61]. The UK guidance suggests further adjustment of the infusion rate, increasing by 1 unit/h if ketone levels are not falling by 0.5 mmol/l/h [3, 27]. The fixed-rate intravenous insulin infusion should be continued until DKA has resolved, by clinical assessment of ketonaemia and acidosis verified by a venous blood gas. If DKA has resolved, but the person is still unable to eat and drink, they can be converted to a variable-rate intravenous insulin infusion with appropriate concomitant glucose-containing infusion fluids.

Uncomplicated DKA can be managed with subcutaneous rapid-acting insulin (e.g. lispro, aspart, glulisine). Appropriate clinical support must be available for frequent glucose monitoring, as the insulin would need to be administered every 1–2 h [56, 57, 60]. Those already on a basal insulin subcutaneously should continue at their usual dose alongside a fixed-rate intravenous insulin infusion [27]. For those newly diagnosed with type 1 diabetes at presentation, it is recommended that they are initiated on a basal insulin subcutaneously (approximately 0.25 units/kg) to provide a safety net for rebound ketosis and facilitate easier transfer to subcutaneous insulin on DKA resolution [27].

Electrolyte considerations

Potassium

There is an estimated total body potassium deficit of 3–5 mmol/kg of body weight in people with DKA. Despite this, measured serum potassium levels are often at or above the upper limits of normal, due to a shift of intracellular potassium to the extracellular space [4, 15, 22, 30]. Correction of the acidosis and concurrent insulin administration will reduce serum potassium levels through the parallel actions of increased cellular potassium uptake in peripheral tissues and increased urinary excretion. A measured serum potassium concentration of <5.0 mmol/l should prompt intravenous replacement of 40 mmol of potassium chloride within each infused litre of fluid, which is usually sufficient to keep the potassium within the normal range of 4–5 mmol/l. Should the potassium fall <3.5 mmol/l, individuals are likely to require more than 40 mmol/h of potassium, which should prompt a senior clinical review. In this case, if the person is being treated outside an ICU setting, the majority of hospital guidelines do not allow the addition of potassium to fluid bags or for >40 mmol/h to be given via peripheral cannulas. The options are to either slow down the rate of insulin per hour (0.05 units/kg/h) to reduce the drive of potassium into the intracellular space or obtain central venous access in an ICU setting where higher concentrations of potassium may be given. Individuals who present with hypokalaemia prior to treatment initiation are difficult to adequately manage outside an ICU setting, because of the likely total body potassium requirements and the likelihood of further serum potassium reduction on treatment initiation with insulin and fluid replacement [27].

Bicarbonate

The administration of intravenous bicarbonate therapy is not routinely recommended, as it does not improve cardiac or neurological function or promote a more rapid rate of recovery from hyperglycaemia and ketoacidosis [62, 63]. Excessive bicarbonate use can increase the risk of hypokalaemia, reduce tissue oxygen uptake (increasing lactate), and potentiate cerebrospinal fluid acidosis due to an increase in CO_2 partial pressure [3, 64]. However, some guidelines and commentaries note that severe acidosis can reduce myocardial contractility and cause cerebral vasodilatation and coma, recommending that with severe metabolic acidosis (pH <6.9) sodium bicarbonate should be administered until the pH rises to 6.9–7.0 [27]. Data from randomized controlled trials to firmly recommend this treatment option are lacking [63, 65].

Phosphate and magnesium

In a process similar to potassium, phosphate will often appear normal prior to DKA treatment initiation, though serum phosphate will decline during treatment due to an overall total body deficit (averaging 1 mmol/kg) [27, 66]. Though severe hypophosphataemia can result in muscle weakness, haemolytic anaemia, and rhabdomyolysis, studies have not shown any benefit of phosphate replacement [66–70]. Hence phosphate replacement should only be suggested for those with cardiac dysfunction, anaemia, and respiratory depression, with a serum concentration <0.3–0.5 mmol/l [3, 27].

Though magnesium deficits are commonly seen in DKA, there is no proven benefit of replacement [71, 72]. Magnesium replacement should be reserved for those with severe hypomagnesaemia and hypocalcaemia, where dose and rate of replacement should follow locally agreed protocols, usually dependent on severity of symptoms.

Complications

Hypoglycaemia and hypokalaemia are the two most common complications during DKA management, but the risk of both can be reduced by careful electrolyte monitoring and the management described previously [61]. Approximately 10–30% of people with type 1 diabetes experience hypoglycaemia during management, most often occurring several hours after intravenous insulin infusion commencement [61]. Omission or delay in appropriate initiation of glucose-containing fluids or where guidelines differ internationally, and not reducing the insulin infusion rate when the glucose level reaches 14 mmol/l (250 mg/dl), are the two commonest causes of hypoglycaemia [3, 61]. Close, frequent glucose monitoring is essential to reduce risk, as many individuals either do not experience the expected typical adrenergic *early-warning* symptoms of sweating, anxiety, hunger, or tachycardia, or those symptoms could be attributed to the stress of the DKA state itself. Acute kidney injury is a common complication of DKA owing to the severe hypovolaemia caused by osmotic diuresis resulting in prerenal failure [4]. Though cerebral injury is a serious complication seen in approximately 1% of children with DKA, it is rarely reported in adults with DKA [73, 74].

Resolution and prevention

The criteria for DKA resolution include venous pH >7.3, serum bicarbonate >18 mmol/l, and ideally a plasma glucose level <11.1 mmol/l (200 mg/dL) [3, 27]. This is when subcutaneous insulin therapy can be resumed or commenced. If a state of DKA persists for more than 24 hours, other contributing factors should be explored, such as alternative causes of raised anion gap metabolic acidosis or problems with insulin delivery.

Given that the half-life of rapid-acting intravenous insulin is 5–7 minutes, it should be appreciated that any sudden interruption to this infusion could result in rebound hyperglycaemia and ketoacidosis [75,76]. Hence, on resolution of DKA, an intravenous insulin infusion should be continued for up to 1–2 hours after subcutaneous insulin is commenced. Continuing subcutaneous basal insulin alongside a fixed-rate intravenous insulin infusion during DKA management can prevent rebound hyperglycaemia after the intravenous insulin infusion is discontinued, which is standard practice in UK guidelines [27,76].

Review by a specialist diabetes team is advised if available. This can help ensure that the individuals' previous insulin regimen remains appropriate in terms of insulin type and doses or advice offered for an insulin-naïve person. Typically, someone new to insulin would be started at a total daily dose of 0.5–0.7 units/kg [3,27,77]. This would usually be administered as a *basal bolus* (once- or twice-daily basal insulin alongside rapid-acting insulin with meals) or twice-daily *fixed mixed* insulin regimen (with morning and evening meals) [3,27,77].

Pregnancy can increase the risk of developing DKA even with relatively lower glucose levels. It is imperative that in cases of DKA presenting in pregnancy, there is specialist input and joint care from the diabetes and obstetrics teams as soon as possible [4,78].

Individuals with end-stage renal failure or on dialysis require specialist input as early as possible after presentation, with special attention paid to their fluid balance. Although this is thankfully rare due to the reduced clearance of insulin, it can sometimes be difficult to distinguish from the chronic metabolic acidosis associated with chronic kidney disease. Recent Joint British Diabetes Societies (JBDS) guidance outlines the clinical considerations necessary for the management of fluids, insulin, and potassium replacement, all of which can contribute to a cacophony of complexity in this clinical scenario [79].

It is also important to ensure that all possible actions are taken to help reduce the risk of recurrent DKA. In the case of suspected contributing mental health issues (e.g. deliberate insulin omission as an act of self-harm, eating disorder) or alcohol-associated problems, support from relevant agencies should be offered. Knowledge of sick-day rules and self-care motivation should be reviewed. The individual should have access to appropriate glucose and ketone monitoring equipment. Educational materials and care plans can also be provided for families and carers, with specialist follow-up or access arranged where indicated. The frequency of hospitalization for DKA has been reduced following diabetes education programmes and with access to diabetes nurses or educators [80].

Hyperosmolar hyperglycaemic state

Commonly previously referred to as hyperglycaemic hyperosmolar non-ketotic coma (HONK), HHS is the other major hyperglycaemic emergency in diabetes. It is characterized by severe dehydration, hyperglycaemia, and hyperosmolarity in the absence of significant ketonaemia [3,81–84]. Though it was associated with a mortality of up to 20%, this has fallen in recent decades, but remains higher than in DKA.

Pathophysiology

The pathophysiology of HHS is illustrated in Figure 41.1 and although similar to that of DKA, there are a few characteristic differences. The predominant picture is of relative insulin deficiency and increased counter-regulatory hormones, which lead to increased gluconeogenesis and reduced glucose uptake in peripheral tissues [1,83]. There remains enough insulin to prevent hepatic free fatty acid oxidation and significant ketogenesis, but not enough to prevent hyperglycaemia and subsequent osmotic diuresis [7,85]. The commonly seen severe hyperglycaemia at diagnosis, often developing over several days, results in prolonged osmotic diuresis, leading to a cycle of worsening dehydration, hyperosmolality, and eventually renal impairment, leading to reduced glucose excretion and further haemoconcentration [1]. Fluid losses are severe, with an estimated deficit of 100–220 ml/kg, although individuals may show only mild signs of volume depletion [3]. Biochemically the extreme dehydration will produce a hyperosmolar clinical picture of severe hypernatraemia, hyperuraemia, and hyperglycaemia, although as in DKA there is a total body deficit of sodium (5–13 mmol/kg), potassium (4–6 mmol/kg), and chloride (5–15 mmol/kg) [3]. In up to 50% of cases HHS and DKA can present as a mixed picture, with a metabolic acidosis due to concurrent ketosis and raised serum lactate levels, and mortality reported as higher in this group (8%) when compared to those with either DKA (3%) or HHS (5%) alone [13,86].

Precipitating factors

HHS is typically a more gradual process that evolves over a number of days to a few weeks, in contrast to DKA that may develop over a few hours. Though most often observed in older people with type 2 diabetes, HHS may also reveal a new presentation of type 2 diabetes in up to 20% of cases [45]. With an increase in the prevalence of obesity, type 2 diabetes is gradually being diagnosed at a younger age and therefore younger adults can also develop HHS, as well as those with type 1 diabetes [87,88]. Infection is the most common precipitant, with urosepsis and pneumonia accounting for up to 50% of cases [89,90]. Other acute situations that release counter-regulatory stress hormones such as surgery, trauma, acute coronary syndromes, or acute stroke can also predispose to HHS. Several medications that cause hyperglycaemia by increasing insulin resistance, such as glucocorticoids and second-generation antipsychotics (clozapine, olanzapine), can precipitate HHS, especially if either appropriate monitoring of capillary glucose levels or screening for new-onset diabetes is omitted [91,92]. Other medications such as phenytoin, thiazide diuretics, protease inhibitors, and β-blockers can also be causative [91] (Table 41.4).

Clinical presentation and diagnosis

The majority of individuals who develop HHS will do so over days to weeks and therefore the progressive onset of symptoms can be difficult to detect until they are severe. The person will often have experienced polyuria, polydipsia, significant dehydration, and a progressive decline in conscious level, ranging from drowsiness to coma. There will be severe dehydration at presentation, usually without signs of acidosis (Table 41.5). The JBDS notes that there is no firm definition of HHS. However, the notable characteristic features would be hypovolaemia, hyperglycaemia (>30 mmol/l; 540 mg/dL), and hyperosmolarity (>320 mosmol/kg), without the

Table 41.4 Causes of hyperosmolar hyperglycaemic state.

New presentation of type 2 diabetes
Medications, e.g. high-dose steroids, second-generation antipsychotics
Alcohol excess
Sepsis/infection
Cerebrovascular disease
Trauma
Long lie following a fall
Reduced fluid intake, e.g. reduced thirst perception in older age
Reduced fluid access

Source: Adapted from Patel 2021 [37] and Akturk et al. [38].

Table 41.5 Diagnostic criteria for hyperosmolar hyperglycaemic state, and definition of resolution.

- Serum osmolality[a] >320 mosmol/kg
- Plasma glucose concentration >30 mmol/l (540 mg/dL)
- pH >7.3
- Serum bicarbonate concentration >15 mmol/l
- Plasma ketones <3 mmol/l (30 mg/dL)
- Hypovolaemia
- Definition of resolution:
  1) Clinical and cognitive status is back to the pre-morbid state
  2) Osmolality <300 mOsm/kg
  3) Hypovolaemia has been corrected (urine output ≥0.5 ml/kg/h)
  4) Blood glucose <15 mmol/l (170 mg/dL)

[a] Calculated serum osmolality = $2[Na^+]$ + glucose + urea.
Source: Adapted from Mustafa et al. 2023 [83].

presence of significant ketonaemia (<3 mmol/l) or acidosis (pH < 7.3, bicarbonate >15 mmol/l). The American Diabetes Association definition is very similar [3, 83]. Many individuals present with a high anion gap metabolic acidosis alongside HHS, which often resolves quickly on treatment initiation [13].

Management

The treatment principles for HHS are similar to those for DKA, namely correction of hypovolaemia, hyperosmolality, and electrolyte disturbances and addressing the precipitating cause (Figure 41.3) [3, 83]. Due to the extreme dehydration, the initial focus of treatment is fluid and electrolyte replacement to restore circulating volume and electrolyte deficit, subsequently diluting sodium, urea, and glucose levels [83]. The infusion of 0.9% sodium chloride at 1000 ml/h for the first 2–3 h is the usual recommendation due to the need to replace fluid, sodium, and chloride. Ongoing fluid choice and rate should be clinically reviewed based on osmolarity, urine output, and electrolyte change in the past 12 h. There is no experimental evidence to suggest that using hypotonic 0.45% sodium chloride to reduce osmolarity is preferable, and this can result in a dangerously rapid drop in serum sodium levels (>10 mmol/l in 24 h) [83]. On initiation of treatment, if the glucose levels are extremely high, there is likely to be an increase in sodium levels as glucose levels drop, but this does not indicate the need to switch to hypotonic intravenous fluids.

Increased serum potassium is often seen in HHS for pathophysiological reasons, as in DKA. With the serum potassium deficit estimated at 3–5 mmol/l of body weight, the principles of potassium replacement are also as for DKA, where potassium replacement should be initiated if serum potassium is <5.5 mmol/l. UK guidelines suggest that fixed-rate intravenous insulin infusion treatment should only be commenced at 0.05 units/kg/h when glucose levels stop falling with fluid replacement, or if the person initially presents with ketonaemia suggesting hypoinsulinaemia [83]. The target range for glucose should be 10–15 mmol/l, which may require the addition of intravenous 5–10% glucose as for DKA management. The ongoing need for insulin or alternative diabetes therapy is reviewed when the person has an improved conscious level and can manage sufficient oral intake [3, 83].

Complications

The hypercoagulable state increases the risk of both arterial and venous thromboembolic events in HHS [3, 93]. Formal prophylactic anticoagulation during treatment is recommended by some groups and noted in the UK guidelines [83]. However, routine use of therapeutic anticoagulation is not recommended [94]. There is an increased risk of foot pressure ulcers developing, and so foot-protection measures should be taken and feet re-examined daily. There are reports of concomitant rhabdomyolysis or subclinical rhabdomyolysis in HHS, where there appears to be a linear relationship with the severity of hyperosmolarity and the serum level of creatinine kinase [95, 96]. As rhabdomyolysis and a raised creatinine kinase can cause acute renal failure, consideration should be given to assessing for this, as it will have an impact on decision making around appropriate fluid management to avoid acute fluid overload [95, 96].

Prevention

Improved education around awareness and risk factors for developing HHS are key to reducing future risk. Ensuring that appropriate access to fluids and glucose monitoring are in place, especially in the context of the precipitants outlined, should also help to reduce the risk of HHS developing.

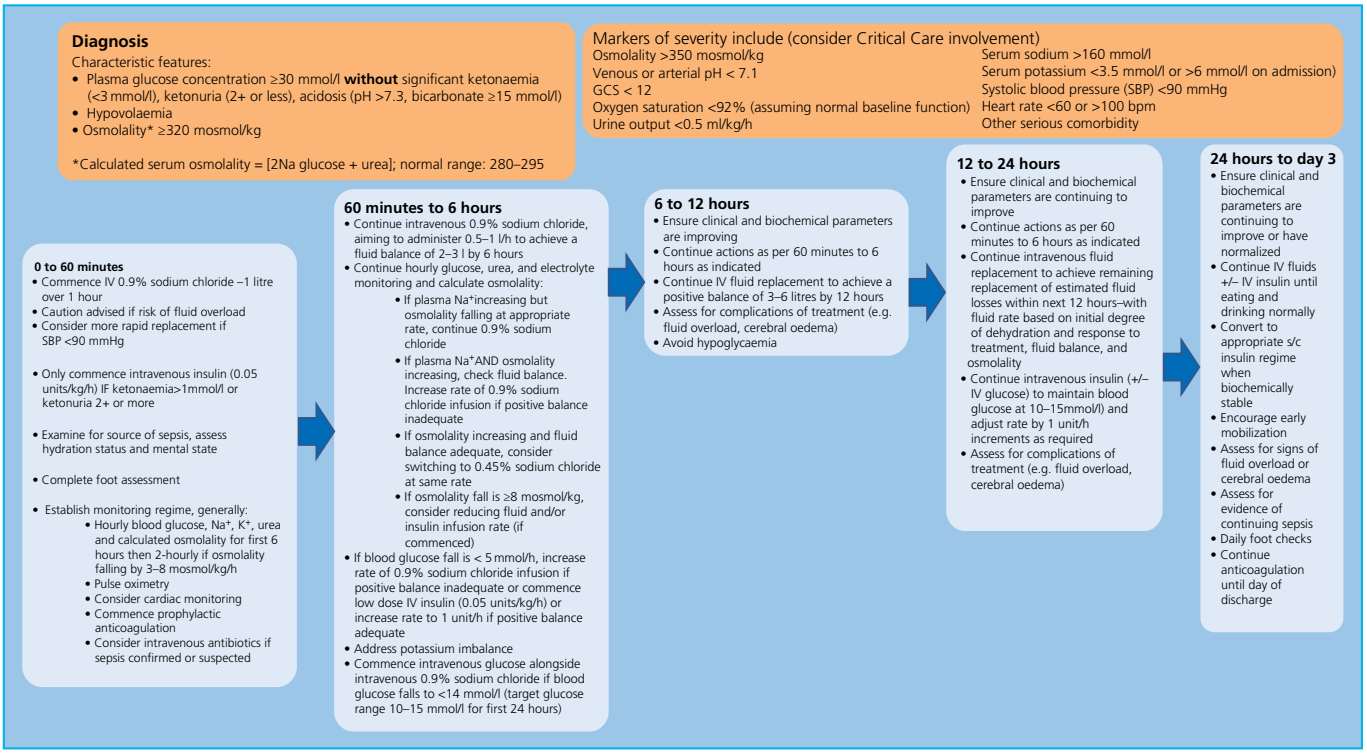

Figure 41.3 Management of hyperosmolar hyperglycaemic state in adults. IV, intravenous; GCS, Glasgow coma score; s/c, subcutaneous; SBP, systolic blood pressure. Source: Adapted by permission from Scott et al. 2015 [82].

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7 Microvascular Complications in Diabetes

42 Pathogenesis of Microvascular Complications

Allan Flyvbjerg
Steno Diabetes Center Copenhagen, Copenhagen, Denmark
Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Key points

- Microvascular complications affect the capillaries and arterioles in the retina (retinopathy), the kidney (nephropathy), and nerves (neuropathy).
- Microvascular complications are caused by prolonged exposure to hyperglycaemia.
- Microvascular complications are best prevented by strict metabolic management.
- Hyperglycaemia damages cell types that cannot downregulate glucose uptake, causing intracellular hyperglycaemia.
- Persistent consequences of hyperglycaemia-induced mitochondrial superoxide production may also explain the continuing progression of tissue damage after improvement of glycaemic levels (hyperglycaemic memory or the legacy effect).
- Different individual susceptibilities to microvascular complications have been linked to genetic polymorphisms.
- Several proven and potential pathogenic factors linking hyperglycaemia to the development of microvascular complications may be categorized into five groups: metabolic factors, haemodynamic factors, growth factors/cytokines, intracellular factors, and the complement system.
- Incretin drugs, which include glucagon-like peptide 1 receptor agonists and dipeptidyl peptidase 4 inhibitors, and sodium–glucose cotransporter 2 inhibitors have proven cardio-renoprotective effects through mechanisms beyond those that can be explained by the blood glucose and/or body weight lowering effects alone.

Diabetic angiopathy: definition and clinical features

Diabetic angiopathy is characterized by functional and structural organ damage as a result of changes in the vascular system. Diabetic angiopathy is divided into *microangiopathy*, which affects the capillaries and arterioles in the retina (retinopathy), the kidney (nephropathy), and nerves (neuropathy); and *macroangiopathy*, which affects arteries in the brain (cerebrovascular disease), heart (ischemic heart disease and congestive heart failure), and the lower extremities (peripheral arterial disease) (Figure 42.1). Diabetic angiopathy has a significant impact on the prognosis, life expectancy, and quality of life of people with diabetes. Late diabetes-related complications may occur both in type 1 diabetes and type 2 diabetes, which is the reason all individuals with diabetes should be examined regularly in an appropriate screening programme. Microvascular complications are quantitatively dominant in type 1 diabetes, whereas macroangiopathy dominates the clinical appearance in type 2 diabetes. In the treatment priorities in the prevention of diabetic angiopathy, microvascular complications are best avoided by strict metabolic management of blood glucose, whereas macrovascular complications are best avoided by strict treatment of dyslipidaemia, hypertension, and other risk factors for cardiovascular disease (Figure 42.2).

The pathogenesis of microvascular complications is described in this chapter, followed by a description of diabetic retinopathy in Chapter 43, diabetic nephropathy in Chapter 44, and diabetic peripheral neuropathy in Chapter 45. The pathogenesis of macrovascular complications, including atherosclerosis in diabetes, is described in Chapter 46, cardiovascular risk factors in diabetes in Chapters 47 and 48, ischaemic heart disease in Chapter 49, heart failure in Chapter 50, cerebrovascular disease in Chapter 51, and peripheral arterial disease in Chapter 52.

A classical morphological feature of diabetes-related microvascular complications (i.e. microangiopathy) is a thickening of the basement membrane in the capillaries and arterioles in the retina, kidney, and nerves. The magnitude of the thickening increases with the duration of diabetes. The thickening of the basement membrane is seen in virtually all individuals with diabetes, but clinically symptomatic organ damage is far less frequent. However, much of the impact of chronic diabetes falls on the microcirculation [1,2]. With long-standing disease, there is progressive narrowing and eventual occlusion of vascular lumina, resulting in impaired perfusion, ischaemia, and dysfunction of the affected tissues. Several processes contribute to microvascular occlusion. One of the earliest is increased vascular permeability, allowing extravasation of plasma proteins that accumulate as periodic acid–Schiff (PAS)–positive deposits in the vessel walls. In addition, extracellular matrix production by perivascular cells such as pericytes (retina) and mesangial cells (glomerulus) is increased, brought about by changes in the synthesis and turnover of its component proteins and glycosaminoglycans. As a result, the basement membrane is thickened in many tissues, including retinal capillaries and the vasa nervorum, along

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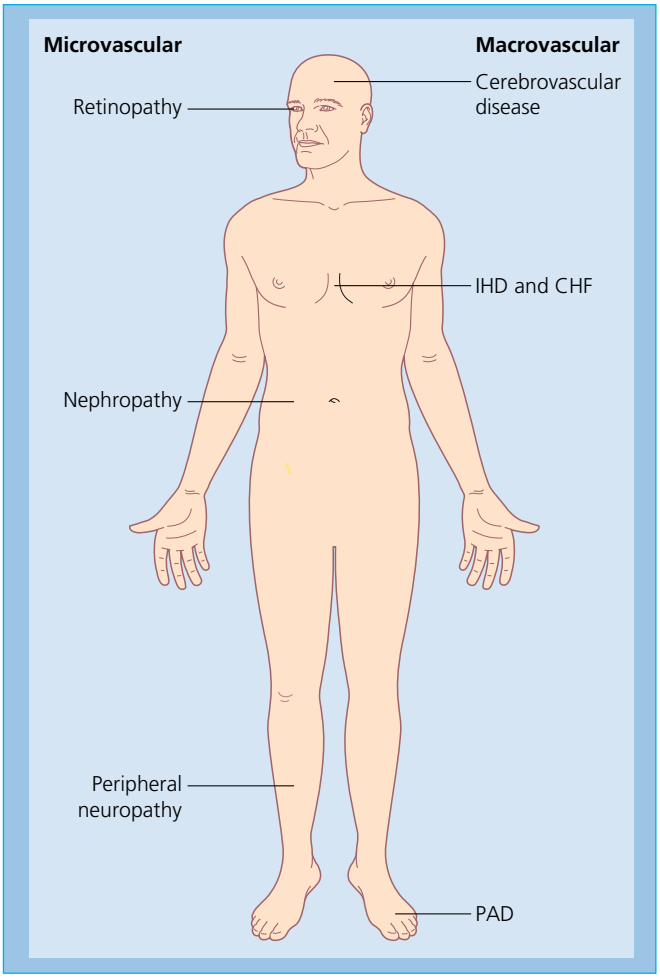

Figure 42.1 Diabetic angiopathy. Diabetic angiopathy is divided into *microangiopathy*, which affects the capillaries and arterioles in the retina (retinopathy), the kidney (nephropathy), and nerves (neuropathy), and *macroangiopathy*, which affects arteries in the brain (cerebrovascular disease), heart (ischaemic heart disease, IHD; and congestive heart failure CHF), and the lower extremities (peripheral artery disease, PAD).

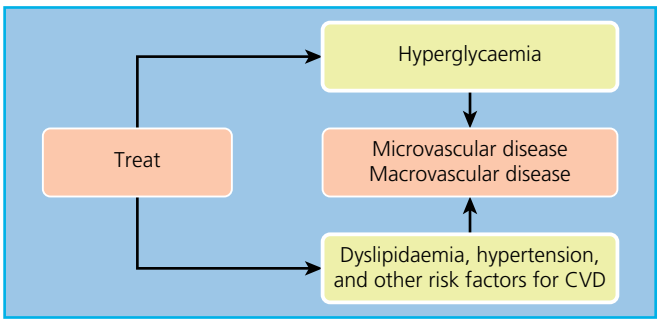

Figure 42.2 Primary priorities in the prevention of diabetic angiopathy. Microvascular complications are best prevented by strict metabolic management of glucose, whereas macrovascular complications are best avoided by strict treatment of dyslipidaemia, hypertension, and other risk factors for cardiovascular disease (CVD). Also read the section in this chapter about the potential mechanisms behind the renoprotective effects of the incretin drugs, glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors, and sodium–glucose cotransporter 2 (SGLT-2) inhibitors.

with mesangial matrix in the renal glomerulus. Hypertrophy and hyperplasia of endothelial, mesangial, and arteriolar smooth muscle cells also contribute to vessel wall thickening. Finally, increased coagulability and adhesion of platelets and leucocytes to the endothelial surface lead to microthrombus formation and luminal occlusion.

The progressive narrowing and blockage of diabetic microvascular lumina are accompanied by loss of microvascular cells. In the retina, diabetes induces apoptosis of Müller cells and ganglion cells [3], pericytes, and endothelial cells [4]. In the glomerulus, widespread capillary occlusion and declining renal function are associated with podocyte loss. In the vasa nervorum of nerves, endothelial cell and pericyte degeneration occurs [5] and appears to precede functional abnormalities of peripheral nerves [6]. Increased apoptosis of cells in the retina, renal glomerulus, and peripheral neurons is a prominent feature of diabetes-related microvascular tissue damage [4, 7–10] and may also damage adjacent cells.

Pathogenesis of microvascular complications: the role of hyperglycaemia

Overall, diabetes-related microvascular complications are caused by prolonged exposure to high glucose levels. This has been established in large-scale prospective studies, both in type 1 diabetes by the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) [11] and in type 2 diabetes by the UK Prospective Diabetes Study (UKPDS) [12]. Similarly, robust data in type 2 diabetes have been reported by the Steno-2 study [13, 14]. In this section, the potential mechanisms of differences in cell response to hyperglycaemia, the phenomenon of glycaemic memory, and determinants of individual susceptibility to hyperglycaemia-induced damage are described.

Differences in cell response to hyperglycaemia

As every cell in the body of an individual with diabetes is exposed to abnormally high glucose concentrations, it may be asked why hyperglycaemia selectively damages some cell types whereas others are unaffected. The targeting of specific cell types by generalized hyperglycaemia reflects the failure of those cells to downregulate their uptake of glucose when extracellular glucose concentrations are elevated. Cells that are not directly susceptible to hyperglycaemic damage, such as vascular smooth muscle, show an inverse relationship between extracellular glucose concentrations and glucose transport. In contrast, vascular endothelial cells, a major target of hyperglycaemic damage, show no significant change in glucose transport rate when the glucose concentration is elevated, resulting in intracellular hyperglycaemia (Figure 42.3) [15]. These differences are caused in part by tissue-specific differences in expression and function of different glucose transporter (GLUT) proteins [16].

Glycaemic memory or legacy effect

In 1993, the results of the landmark DCCT study showed that, in individuals with short-duration type 1 diabetes, intensive glycaemic management dramatically reduced the occurrence and severity of microvascular complications. After the announcement of the DCCT results, many participants who had been in the standard therapy group adopted more intensive therapeutic regimens,

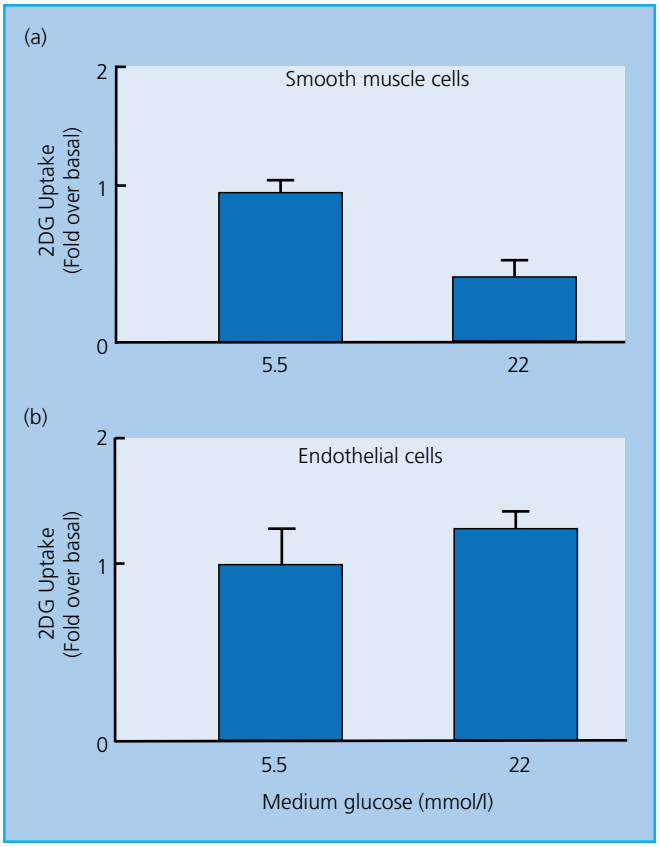

Figure 42.3 Lack of downregulation of glucose transport by hyperglycaemia in cells affected by diabetes-related complications. (a) 2-Deoxyglucose (2DG) uptake in vascular smooth muscle cells pre-exposed to 5.5 or 22 mmol/l glucose; (b) 2DG uptake in aortic endothelial cells pre-exposed to 5.5 or 22 mmol/l glucose. Source: Data from Kaiser et al. 1993 [15].

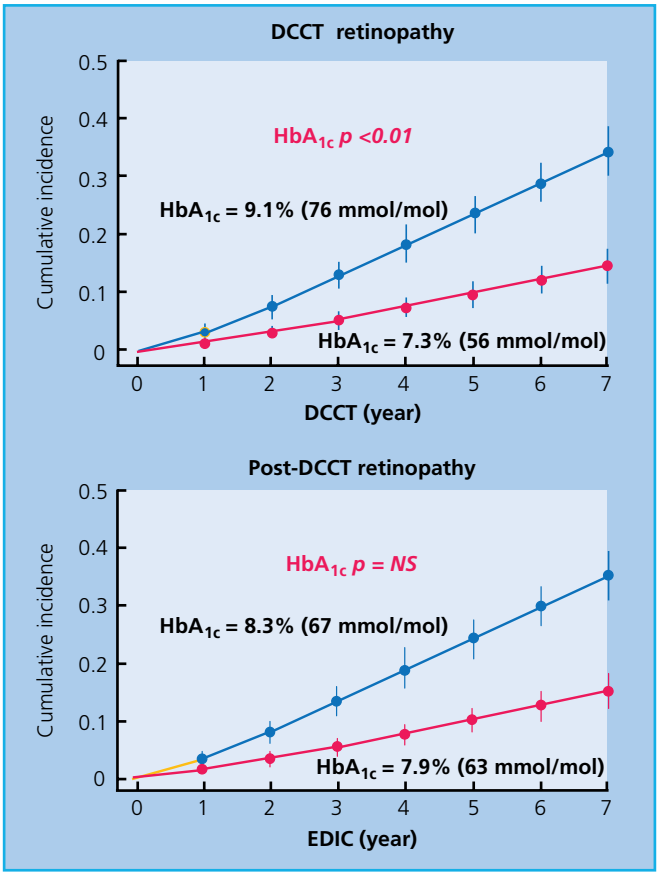

Figure 42.4 Hyperglycaemic memory. Previous higher blood glucose levels make individuals with diabetes more susceptible to damage despite subsequent lower blood glucose exposure. After the end of the Diabetes Control and Complications Trial (DCCT), the group treated with conventional insulin therapy (blue) continued to have a higher incidence of diabetic retinopathy than the intensively managed group (red), even though post-trial glycated haemoglobin (HbA_{1c}) was comparable in the two groups. Reported HbA_{1c} is the mean in each group. EDIC, Epidemiology of Diabetes Interventions and Complications study.

and their glycaemic levels improved, as measured by glycated haemoglobin (HbA_{1c}). At the same time, the mean HbA_{1c} worsened for those who had been in the intensive therapy group. The post-DCCT HbA_{1c} values for both groups became statistically identical for the following 14 years of the EDIC study.

Surprisingly, however, the effects of a 6.5-year difference in HbA_{1c} during the DCCT on the incidence of retinopathy and nephropathy persisted and became greater over the subsequent 14 years of follow-up. Individuals in the standard therapy group continued to have a higher incidence of complications, even with an improvement in glycaemia during the 14 years of EDIC, whereas individuals in the intensive therapy group continued to have a lower incidence of complications, even with deterioration in glycaemia during the EDIC years. This phenomenon has been termed *glycaemic memory* or the *legacy effect* (Figure 42.4). Glycaemic memory also occurs in people with type 2 diabetes. The tight glucose management group from the UKPDS demonstrated a continued reduction in microvascular risk and emergent risk reductions for acute myocardial infarction and death from any cause, despite an early loss of glycaemic differences. A continued benefit was evident during the 10-year post-trial follow-up among overweight participants [17–19].

Glycaemic memory has several important clinical implications and recommendations:

- Early and tight metabolic management is required to prevent long-term diabetes-related complications.
- Tight metabolic management after long-term metabolic dysregulation may not prevent the subsequent development of microvascular complications.
- There is a need for the development of novel therapies that reverse hyperglycaemic memory.

Hyperglycaemia-induced mitochondrial superoxide production may provide an explanation for the continuing progression of tissue damage after the correction of hyperglycaemia (*hyperglycaemic memory*). Post-translational modifications of histones cause chromatin remodelling and changes in gene expression [20–22]. Because these modifications do not involve differences in DNA sequence, they are called *epigenetic* (Figure 42.5a). Transient hyperglycaemia induces long-lasting activating epigenetic changes in the promoter of the Fib-subunit p65 in human aortic endothelial cells (16 hours' exposure) and in aortic cells *in vivo* in non-diabetic mice (6 hours' exposure), which cause sustained increases in p65 gene expression (Figure 42.5b) and in the expression of p65-dependent pro-inflammatory genes. Both the epigenetic changes and the gene expression changes persist for at least six days of subsequent normal glycaemia. Hyperglycaemia-induced epigenetic changes and increased p65 expression are prevented by normalizing mitochondrial superoxide production or superoxide-induced methylglyoxal (Figure 42.5b, c) [23].

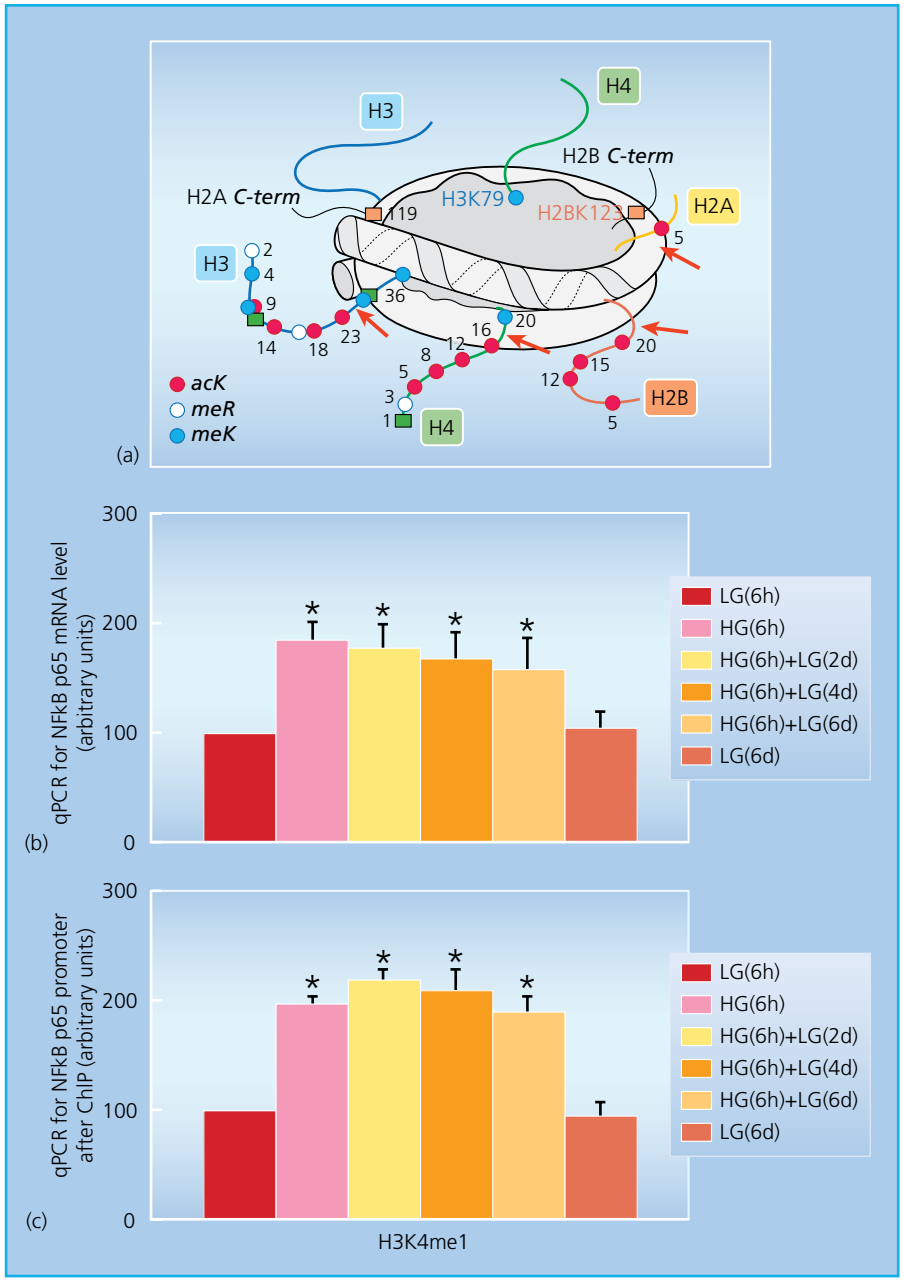

Figure 42.5 Transient hyperglycaemia causes persistent epigenetic changes and altered gene expression during subsequent normoglycaemia. (a) Schematic representation of several histone modifications. (b, c) Transient hyperglycaemia induces persistent increased expression of the NFκB p65 subunit, caused by persistent epigenetic changes, including histone 3 lysine 4 mono-methylation (H3K4me1) in the proximal promoter of the NFκB p65 subunit. acK, acetylated lysine; HG, high glucose; LG, low glucose; meK, methylated lysine; meR, methylated arginine; ChiP, chromatin immunoprecipitation. Source: Data from El-Osta et al. 2008 [23].

These results highlight the dramatic and long-lasting effects that short-term hyperglycaemic spikes can have on vascular cells and suggest that transient hyperglycaemic spikes may be an HbA_{1c}-independent risk factor for diabetes complications. Demethylation of another histone lysine residue, H3K9, is also induced by hyperglycaemia-induced overproduction of reactive oxygen species (ROS). This reduces inhibition of p65 gene expression, and thus acts synergistically with the activating methylation of histone 3 lysine 4 [24]. Consistent with these observations, others have shown similar epigenetic changes in lymphocytes from individuals with type 1 diabetes [25] and in vascular smooth muscle cells derived from an experimental mouse model of type 2 diabetes [26].

Determinants of individual susceptibility to hyperglycaemia-induced damage

As with all complex diseases, the occurrence and progression of diabetes complications vary markedly among people with diabetes. Some have type 1 diabetes for over 50 years with minimal complications, whereas others manifest severe disease or death within 15 years after diagnosis. The management of blood glucose, and also blood pressure and lipid profile, is an important factor in predicting the risk of complications, but it only partially explains the risk of complications for an individual. Therefore, genetic factors have been investigated for their influence on the risk of developing complications. An understanding of the genes involved in the susceptibility to or protection from diabetes complications can lead

both to a better understanding of the pathophysiological mechanisms and to new biomarkers and molecular targets for drug development. Familial clustering studies strongly support a role for genetic determinants of susceptibility to hyperglycaemic damage.

In two studies of families that have two or more siblings with type 1 diabetes, if one sibling had advanced diabetic nephropathy, the other sibling with diabetes had a nephropathy risk of 72–83%. By contrast, the risk was only 17–22% if the index sibling did not have diabetic nephropathy [27,28]. Numerous associations have been made between various genetic polymorphisms and the risk of different diabetes complications. These include HLA-DQB10201/0302 alleles [29], polymorphisms of the aldose reductase gene [30], the sorbitol dehydrogenase gene [31], and the promoter of erythropoietin gene [32]. A positive linkage and association with diabetic nephropathy of simple tandem-repeat polymorphisms and single-nucleotide polymorphisms (SNPs) in 20 genes have been demonstrated in families of individuals with type 1 diabetes of white European descent [33]. Three genes code for growth factors or growth factor receptors, five genes code for intracellular factors, three genes code for components of the extracellular matrix, and two genes are involved in its degradation. The remaining genes are likely to be important in kidney function [33]. The DCCT/EDIC trial also reported familial clustering and association with gene polymorphisms. In those with diabetes, the odds ratio for risk of severe retinopathy was 5.4-fold higher in family members of participants with retinopathy than in those without; coronary artery calcification also showed familial clustering [34]. In the same cohort, an association of multiple superoxide dismutase 1 variants was associated with the development and progression of diabetic nephropathy [35].

In the future, the challenge will be to identify specific genes involved in the varying clinical severity of diabetes complications. Recent emphasis in human disease genetics has been on so-called modifying genes; that is, genetic variants that are distinct from disease susceptibility genes but modify the phenotypic and clinical expression of the disease. Studies show that genetic modifiers can be *tipping-point* genes. This means that one gene changes the whole phenotype in an all-or-nothing fashion, in contrast to the incremental effects seen with changes in a large number of non-modifier genes. Many examples of modifier genes are known in model organisms, and several have been identified in humans [36,37].

Beyond hyperglycaemia

It has become increasingly evident that several different pathways play a role as mediators between elevated and fluctuating blood glucose levels and the development of microvascular complications. The number of systems and interactions between these factors are complex, but as described in a review article dealing with the pathogenesis of diabetes-related kidney disease, four important groups of mediators are metabolic factors, haemodynamic factors, growth factors/cytokines, and intracellular factors [38]. Furthermore, there is an important role for the innate immune system. Figure 42.6 provides a schematic depiction of the potential hierarchy and interactions between metabolic, haemodynamic, growth factors/cytokines, intracellular factors, and the innate immune system in the pathogenesis of microvascular complications. In the following section, the five systems and the evidence for their role are described in more detail. The last part of this section proposes the potential mechanisms behind the renoprotective effect of incretin drugs and sodium–glucose cotransporter 2 (SGLT-2) inhibitors in the treatment of type 2 diabetes (Chapter 44).

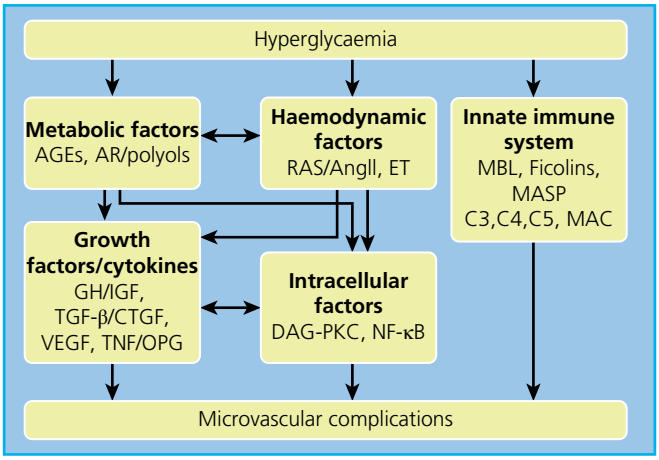

Figure 42.6 Schematic depiction of pathogenetic factors in microvascular complications showing the potential hierarchy and interactions between metabolic, haemodynamic, growth factors/cytokines, intracellular factors, and the innate immune system. AGEs, advanced glycation end-products; AngII, angiotensin II; AR, aldose reductase; C3, C4, C5, complement C3, C4, C5; CTGF, connective tissue growth factor; DAG–PKC, diacylglycerol–protein kinase C; ET, endothelin; GH, growth hormone; IGF, insulin-like growth factor; MAC, membrane attack complex; MASP, MBL-associated serine protease; MBL, mannose-binding lectin; NFκB, nuclear factor κB; OPG, osteoprotegerin; RAS, renin–angiotensin system; TGF-β, transforming growth factor β; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor.

Metabolic factors

Among the different metabolic pathways that have impacts on the development of microvascular complications, the roles of advanced glycation end-products (AGEs) and of the aldose reductase/polyol pathway have been studied in most detail.

Advanced glycation end-products

Amadori products are formed when glucose and other reactive carbonyl compounds react non-enzymatically with proteins, lipids, or nucleic acids and Schiff bases. Additional rearrangements and modifications lead to the generation of various forms of AGEs, such as carboxymethyllysine, pentosidine, imidazolone, and pyrraline [38,39]. AGEs interact with specific receptors [39–41]: p60 (OST-48, AGE-R1), p90 (80K-H, AGE-R2), galectin-3 (AGE-R3), the macrophage scavenger receptor type II (ScR-II), and CD36 all regulate the uptake and clearance of AGEs [39,41]. The best-characterized receptor is the receptor for AGEs (RAGE) [39]. AGEs can also act in a receptor-independent way by cross-linking proteins [39,40]. AGEs alter the structure and function of intra- and extracellular molecules, increase oxidative stress, and modulate cell activation, signal transduction, and the expression of cytokines and growth factors through receptor-dependent and -independent pathways [39–41].

Pre-clinical data in support of a role for AGEs in microvascular complications come from studies in diabetic animal models [38,42]. Renal AGE levels are increased in long-term experimental diabetes [43,44]. Furthermore, in models of type 1 diabetes and type 2 diabetes,

the intake of food-derived AGEs accelerates renal changes, whereas a low-AGE diet provides protection against kidney damage [45]. In animal models of both type 1 diabetes [46,47] and type 2 diabetes, elevated RAGE glomerular podocyte staining has been reported, compared with animals without diabetes [48]. Finally, diabetic transgenic mice overexpressing human RAGE present with kidney and glomerular hypertrophy, increased albuminuria, mesangial expansion, advanced glomerulosclerosis, and increased impaired kidney function, compared with controls [49]. In clinical studies, AGEs have been shown to be elevated in both type 1 diabetes and type 2 diabetes [50,51]; it is important to note, however, that at these concentrations AGEs are not the major ligand for RAGE. Rather, several pro-inflammatory protein ligands have been identified that activate RAGE at low concentrations. These include several members of the S100 calgranulin family and high-mobility group box 1 (HMGB1), all of which are increased by hyperglycaemia. Binding of these ligands with RAGE causes cooperative interaction with the innate immune system signalling molecule toll-like receptor 4 (TLR-4) [52,53].

Targeting the advanced glycation end-product system

Various agents have been examined in attempts to interfere with AGE formation or the cross-linking of proteins by AGEs. Agents that block AGE formation by scavenging reactive carbonyl intermediates include aminoguanidine, pyridoxamine, 2,3-diaminophenazine, OPB-9195, and tenilsetam. ALT-711 is an example of an AGE cross-link breaker. Ways to block the signal transduction through RAGE can be achieved by the use of RAGE antibodies, antisense oligodeoxynucleotides (AS-ODNs), or soluble RAGE [38,42]. Clinical trials have been performed aimed at exploring the clinical effects of pyridoxamine in both type 1 diabetes and type 2 diabetes [54,55]. In one study of mild to moderate renal impairment, the intervention reduced the slope of creatinine change without having an influence on urinary albumin excretion [54]. In another study of more severe renal impairment, there was no effect of treatment, suggesting that treatment should be administered before the onset of significant pathological organ changes [55].

Aldose reductase/polyol pathway

The polyol pathway is based on a family of aldo-keto-reductase enzymes, which can utilize a wide variety of sugar-derived carbonyl compounds as substrates and reduce these by nicotinamide adenine dinucleotide phosphate (NADPH) to their respective sugar alcohols (polyols). The classic representation holds that glucose is converted to sorbitol, and galactose to galactitol. Sorbitol is then oxidized to fructose by the enzyme sorbitol dehydrogenase, with NAD^+ being reduced to NADH. The first and rate-limiting step of the polyol pathway is regulated by aldose reductase, which is found in tissues such as nerve, retina, lens, glomerulus, and blood vessel wall. In these tissues, glucose uptake is mediated by GLUT proteins other than GLUT4 and so does not require insulin; intracellular glucose concentrations therefore rise in parallel with hyperglycaemia.

Several mechanisms have been proposed to explain how hyperglycaemia-induced increases in polyol pathway flux could damage the tissues involved. These include sorbitol-induced osmotic stress, decreased cytosolic Na/K^+-ATPase activity, increased cytosolic $NADH/NAD^+$, and decreased cytosolic NADPH. It was originally suggested that intracellular accumulation of sorbitol, which does not diffuse easily across cell membranes, could result in osmotic damage, but it is now clear that sorbitol levels in diabetic vessels and nerves are far too low to do this. Another early suggestion was that increased flux through the polyol pathway led to decreased phosphatidylinositol synthesis, and that this inhibited Na/K^+-ATPase activity. The latter abnormality occurs in diabetes, but has subsequently been shown to result from hyperglycaemia-induced activation of protein kinase C (PKC), which increases the production of two inhibitors of Na/K^+-ATPase, arachidonate and prostaglandin E2 [56].

The reduction of glucose to sorbitol by NADPH consumes the latter. NADPH is a cofactor required to regenerate reduced glutathione; as glutathione is an important scavenger of ROS, this could induce or exacerbate intracellular oxidative stress. Indeed, overexpression of human aldose reductase increased atherosclerosis in diabetic mice and reduced the expression of genes that regulate the regeneration of glutathione [57]. Reduced glutathione is depleted in the lens of transgenic mice that overexpress aldose reductase and in diabetic rat lens compared with non-diabetic lens [58,59]. Decreased glutathiolation of cellular proteins is related to decreased nitric oxide availability in diabetic rats, which would decrease *S*-nitrosoglutathione. Restoring the nitric oxide levels in experimental animal models of diabetes increases glutathiolation of cellular proteins, inhibits aldose reductase activity, and prevents sorbitol accumulation. Moreover, hyperglycaemia can also inhibit glucose-6-phosphate dehydrogenase, the major source of NADPH regeneration, which may further reduce the NADPH concentration in some vascular cells and neurons [60]. In diabetic vascular cells, however, glucose does not appear to be the substrate for aldose reductase, because the Michaelis constant (K_m) of aldose reductase for glucose is 100 mmol/l, whereas the intracellular concentration of glucose in the diabetic retina is 0.15 mmol/l [61,62]. Glycolytic metabolites of glucose such as glyceraldehyde-3-phosphate, for which aldose reductase has much higher affinity, may be the physiologically relevant substrate.

Targeting the aldose reductase/polyol pathway

Several aldose reductase inhibitors have been developed and studied in experimental and clinical studies for their potential effect on microvascular complications [63], but these drugs have not shown convincing clinical effects [64].

Haemodynamic factors

Tight control of blood pressure delays the progression of retinopathy and nephropathy, whereas elevated blood pressure accelerates the onset of nephropathy and its progression [64–66]. Blockade of the renin–angiotensin system, and thereby the effects of the vasoconstrictor angiotensin II (AngII), is gold-standard treatment and a cornerstone in the secondary and tertiary treatment of incipient or overt microvascular complications, in particular retinopathy (Chapter 43) and nephropathy (Chapter 44). In addition to the well-known systemic and locally haemodynamic effects, the renin–angiotensin system and the endothelin (ET) system may exert non-haemodynamic effects through autocrine and paracrine actions. In the following section, the endothelin system and its role in microvascular complications are addressed.

Endothelin

The endothelin system embraces ET-1–3 and two receptors, of which ET-1 is the most potent vasoconstrictor [67,68]. In mammals, two receptors, ET_A and ET_B, exert their signal mainly through activation of G-proteins. The ET_A receptor is mainly involved in

vasoconstriction and cell proliferation, whereas the ET_B receptor induces nitric oxide release and vasodilation [67,68]. Endothelin acts through paracrine and autocrine actions.

Targeting the endothelin pathway

The effects of endothelins can be blocked by the administration of non-selective endothelin receptor antagonists (e.g. bosentan), selective ET_A antagonists (e.g. avosentan, atrasentan), or ET_B antagonists. As summarized in a recent review [69], endothelin receptor blockade, in particular by the use of selective ET_A blockers, has renoprotective effects in experimental animal models of diabetes, by lowering urinary albumin excretion, podocyte loss, and inflammation. In human diabetes, some renoprotective effects have been reported with bosentan treatment [70] or treatment with selective ET_A blockers [71,72]. However, fluid retention has been a challenge in most studies, which may reduce the future potential for this class of drugs in the treatment of microvascular complications [69].

Growth factors/cytokines

Of the many known growth factors and cytokines, growth hormone (GH) and insulin-like growth factor I (IGF-I) were the first to be implicated in the development of diabetes-related microangiopathy [73–75]. The evidence for a role of GH/IGF-I in its pathogenesis is reviewed elsewhere [38]. So far, no drugs with effects on this axis have yet made it to clinical use. Transforming growth factor β (TGF-β), connective tissue growth factor (CTGF), and vascular endothelial growth factor (VEGF) have been studied intensively over several decades as significant pathogenic factors for diabetic microangiopathy. In recent years, the role of the tumour necrosis factor (TNF) superfamily has been increasingly associated with a pathogenic role in microvascular complications.

Transforming growth factor/connective tissue growth factor

The TGF-β superfamily comprises multifunctional cytokines, where TGF-β1, TGF-β2, and TGF-β3 are involved in extracellular matrix synthesis [76]. The biologically active isoforms are generated after proteolytic activation [76]. Three TGF-β receptors have been identified and TGF-β signal transduction involves at least three subclasses of Smad proteins [76–78]. CTGF is a downstream mediator of TGF-β [37]. There is a huge amount of pre-clinical and clinical evidence that the TGF-β superfamily, including CTGF, may be involved in the pathogenesis of diabetic nephropathy and retinopathy [38,79,80].

Targeting transforming growth factor β and connective tissue growth factor

Clinical studies have been conducted to examine the effects of TGF-β or CTGF blockade. A phase II clinical study has been performed with the application of a TGF-β antibody in individuals with type 1 diabetes and diabetic nephropathy, showing a minor effect on the rise in serum creatinine [81]. Pirfenidone, a compound that blocks TGF-β promoter activity, has been examined in individuals with type 1 diabetes and type 2 diabetes and kidney disease, already on renin–angiotensin system blockade, and demonstrated a beneficial effect on estimated glomerular filtration rate (eGFR) compared with placebo; however, there was a high dropout rate in the pirfenidone-treated participants [82]. In addition to a series of pre-clinical studies showing positive results on kidney variables by blocking the CTGF axis, a single clinical trial has been performed with the application of a human monoclonal antibody to CTGF (FG-3019) in people with diabetic nephropathy [83]. The treatment was generally well tolerated and reduced urinary albumin excretion [83].

Although the promising renoprotective results from pre-clinical studies have facilitated the first clinical studies in individuals with renal impairment, the safety and efficacy of using TGF-β and CTGF blockers in the clinical management of microvascular complications are still uncertain.

Vascular endothelial growth factor

The VEGF family embraces different isoforms and exists in several homodimeric glycoproteins [84,85]. VEGF increases vascular permeability and has a stimulatory effect on endothelial cell differentiation and proliferation [85]. The two well-described VEGF receptors (VEGFR-1 and VEGFR-2) are high-affinity transmembrane tyrosine kinase receptors [85]. The production of VEGF is regulated by other growth factors and cytokines, including IGF-I [84,85]. Numerous pre-clinical and clinical studies have been published in the last two decades, indicating a pathogenic role of VEGF in both diabetic nephropathy [38,86] and retinopathy [87].

Targeting the vascular endothelial growth factor system

Several VEGF/VEGFR antagonists have been developed, including agents that directly block the VEGF peptide, such as an anti-VEGF aptamer (pegaptanib), a monoclonal antibody fragment (ranibizumab), and a full-length VEGF antibody (bevacizumab). Other agents include a soluble VEGF receptor analogue (VEGF-Trap) and small interfering RNA drugs (bevasiranib and rapamycin). Although anti-VEGF treatment halts the development of renal changes in experimental models of type 1 diabetes and type 2 diabetes [38], anti-VEGF treatment has not yet been introduced in the clinic to prevent nephropathy. By contrast, local application of anti-VEGF agents in the eye is a widely used procedure in the management of proliferative diabetic retinopathy, macular oedema and their associated complications [86,87] (Chapter 43).

The tumour necrosis factor superfamily

The TNF superfamily comprises structurally related proteins involved in processes such as regulation of immune response, inflammation, and cell death [88]. TNF-related apoptosis-inducing ligand (TRAIL; also called TNF ligand superfamily member 10) was initially identified as a third member of the TNF superfamily to induce apoptosis [89]. In contrast to other members of the TNF superfamily, TRAIL binds to a complex system of TRAIL receptors. Different TRAIL receptors have been described in humans, four of which are membrane bound: TRAIL-R1 to TRAIL-R4 [88,89]. A fifth receptor is osteoprotegerin. In addition to being a stimulator of the various TRAIL receptors, TRAIL is also an inhibitor of osteoprotegerin. Osteoprotegerin was originally known as an inhibitor of bone resorption binding to the receptor activator of nuclear factor κB ligand (RANKL) [89–91]. Osteoprotegerin acts as a soluble inhibitor of the interaction between RANKL and RANK and also of osteoclastogenesis. Therefore, osteoprotegerin acts as an inhibitor of both TRAIL and RANKL, and the delicate balance between these three components is important both in normal physiology and in pathophysiology [92].

Research on the role of TRAIL in microvascular complications is in its initial phase [87], while an increasing number of studies have been carried out on the role of osteoprotegerin. It has become increasingly clear that osteoprotegerin may play an important role in vascular dysfunction in diabetes, although it was originally

identified as a bone molecule, with an inhibitory effect on osteoclast formation [89,90]. Some studies, on the one hand, indicate that osteoprotegerin may be involved in the development of vascular calcifications [93–95]. Thus, osteoprotegerin appears to be a survival factor for endothelial cells [96]. In addition, osteoprotegerin knockout mice develop vascular calcifications [97]. However, most studies are in support of a pro-atherosclerotic role for osteoprotegerin in the vasculature, which may be particularly pronounced in diabetes. Accordingly, increased circulating osteoprotegerin levels have been observed in studies of experimental diabetes [98,99], and microarray studies in human diabetes specimens have shown upregulation of osteoprotegerin mRNA levels in kidney samples [100,101]. Plasma osteoprotegerin levels correlate with the presence of renal dysfunction or cardiovascular disease in type 1 diabetes and type 2 diabetes [88], and plasma osteoprotegerin levels are associated with vascular endothelial dysfunction [102]. Several prospective studies have focused on circulating osteoprotegerin as a putative predictor of the progression of end-stage renal disease. In individuals with type 1 diabetes and nephropathy, plasma osteoprotegerin is a powerful and independent predictor of progression to end-stage renal disease, cardiovascular, and all-cause mortality [103].

Intracellular factors

Among many different intracellular factors, there has been a particular focus on the potential role of the activation of the diacylglycerol–PKC pathway in the development of microvascular complications.

Diacylglycerol–protein kinase C pathway

PKC is an important intracellular pathway that can be activated by many upstream factors in the development of microvascular lesions, including metabolic, haemodynamic, and growth factor/cytokine factors. PKC can then be a stimulus for the initiation of several growth factors and cytokines. PKC comprises at least 11 isoforms that are widely distributed in mammalian tissues. The activity of the classic isoforms is dependent on both Ca^{2+} ions and phosphatidylserine and is greatly enhanced by diacylglycerol. Persistent and excessive activation of several PKC isoforms might also operate as a third common pathway mediating tissue injury induced by hyperglycaemia and associated biochemical and metabolic abnormalities. This results primarily from enhanced *de novo* diacylglycerol synthesis from glucose via triose phosphates, whose availability is increased because raised intracellular glucose levels enhance glucose flux through the glycolytic pathway [104–107]. Finally, the enhanced activity of PKC isoforms could also result from the interaction between AGEs and their cell-surface receptors [108]. Hyperglycaemia primarily activates the β and δ isoforms of PKC, both in cultured vascular cells [109–111] and in the retina and glomeruli of diabetic animals [105–107], but increases in other isoforms have also been found, such as PKC-α and PKC-ε isoforms in the retina [104] and PKC-α and PKC-δ in the glomerulus of diabetic rats [112,113].

In early experimental diabetes, activation of PKC-β isoforms mediates the diabetes-related decreases in retinal and renal blood flow [114], perhaps by depressing the production of the vasodilator nitric oxide and/or increasing ET-1, a potent vasoconstrictor. PKC overactivity has been implicated in the decreased nitric oxide production by the glomerulus in experimental diabetes [115] and by smooth muscle cells in the presence of high glucose levels [116], and inhibits insulin-stimulated expression of endothelial nitric oxide synthase (eNOS) in cultured endothelial cells [102]. Hyperglycaemia increases the ability of endothelin-1 to stimulate mitogen-activated protein kinase (MAPK) activity in glomerular mesangial cells, and this occurs by activating PKC isoforms [117]. The increased endothelial cell permeability induced by high glucose levels in cultured cells is mediated by activation of PKC-α [118]; activation of PKC by high glucose also induces expression of the permeability-enhancing VEGF in smooth muscle cells [119]. In addition to mediating hyperglycaemia-induced abnormalities of blood flow and permeability, PKC activation may contribute to the accumulation of microvascular matrix protein by inducing expression of TGF-β1, fibronectin, and type IV collagen in both cultured mesangial cells [120,121] and in glomeruli of diabetic rats [112]. This effect appears to be mediated through the inhibition of nitric oxide production by PKC [122]. Hyperglycaemia-induced activation of PKC has also been implicated in the overexpression of the fibrinolytic inhibitor plasminogen activator inhibitor 1 (PAI-1) [123], and in the activation of nuclear factor κB (NFκB) in cultured endothelial cells and vascular smooth muscle cells [124].

Targeting the diacylglycerol–protein kinase c system

Over the last few decades, several PKC inhibitors have been developed and examined in an attempt to lower PKC activity. Ruboxistaurin mesylate, which is a highly specific blocker of PKC-β isoforms and the most widely studied specific PKC inhibitor, has been examined in diabetic animal models and a few pilot studies in humans [125]. These studies showed some beneficial effects on the development of diabetic renal changes in animals, but studies in humans have predominantly been inconclusive [125]. Therefore, the clinical effects of lowering PKC activity in the prevention of microvascular complications remain unclear at present.

Innate immune system

The innate immune or complement system plays an important role in the pathogenesis of diabetes-related microvascular complications [88,126]. The complement system has a key role in facilitating the clearance of microbes and damaged cells by antibodies and phagocytic cells. Activation of the complement system typically occurs through three pathways:

- The lectin pathway, which is triggered by carbohydrates on cell surfaces.
- The classical pathway, which involves antibody-mediated activation via the C1 complex.
- The alternative pathway, which involves direct activation of C3 through surface-binding or tick-over [126].

Activation of any one of these pathways leads to the production of complement C3 convertase, which activates complement component C3, leading to generation of the opsonic C3b and eventually generation of the membrane attack complex (MAC), which lyses, damages, or activates target cells.

Mannose-binding lectin (MBL) is considered the classic activator of the lectin pathway, although studies have shown that a group of pattern-recognition molecules called ficolins (including H-ficolin, L-ficolin, M-ficolin) can also activate the lectin pathway [126–131]. Initiation of the lectin pathway occurs when MBL binds to glycan-associated mannose or ficolins bind to N-acetylglucosamine, N-acetylgalactosamine, or N-acetylneuraminic acid residues on microbial surfaces [127]. Such binding activates MBL-associated serine proteases (MASPs), leading to cleavage of the complement components C2 and C4 and formation of a C4b2b C3 convertase [128]. Activation of the classical pathway

occurs through the formation of an antigen–antibody complex via the C1q domain of complement C1. C1 is a non-covalent complex of three different proteins (C1q, C1r, and C1s) and after the mentioned complex formation C1q subsequently activates C1r and C1s, which then cleave C2 and C4, also leading to formation of the C4b2b C3 convertase. The alternative complement pathway is activated in an antibody-independent manner on foreign surfaces, such as those of viruses, bacteria, and biomaterials, and leads to the subsequent production of a C3bBb C3 convertase. The C3b fragment generated by any of the complement pathways can bind factor B (FB) and, facilitated by factor D (FD), can form the alternative pathway C3bBb C3 convertase, thereby amplifying the complement cascade [129]. Finally, the alternative pathway is constitutively activated at a low level by the continuous hydrolysis of C3, producing an intermediate that forms alternative pathway-initiating C3 convertases with FB and FD via a mechanism known as tick-over. Following cleavage of C3 to C3a and C3b, the three pathways merge to follow a single pathway. The C3b fragments bind to C3 convertases to produce a C5 convertase, which in turn divides C5 further into C5a and C5b. Thus, C6–9 bind to C5b to form the MAC [126, 130].

The evidence for a connection between the complement system and especially renal dysfunction spans decades, and is supported by findings from both experimental and clinical studies [126, 132–135]. Two main mechanisms explain the involvement of complement in the development of nephropathy. First, activation of the lectin pathway occurs following binding of pattern-recognition molecules to proteins that are glycated as a result of exposure to sugars [136, 137]. Second, hyperglycaemia induces glycation of complement-regulatory proteins [138, 139], leading to dysfunction of their regulatory capacity, which in turn might facilitate complement auto-attack; that is, overactivation of complement pathways [137, 139]. These pathophysiological mechanisms are described in further detail in the following sections. In *in vitro* studies, it has been suggested that diabetes-induced alterations in glycoproteins may stimulate complement activation through binding of MBL to neo-epitopes [136, 137]. These diabetes-induced changes may develop either through altered enzymatic protein glycosylation or by a non-enzymatic formation of AGEs [136, 137].

Mannose-binding lectin

Experimental studies have demonstrated a causal relationship between MBL and diabetic nephropathy. Compared to wild-type mice with streptozotocin-induced diabetes (a model of type 1 diabetes), diabetic MBL-knockout mice have less renal damage, with reduced renal hypertrophy, urinary albumin excretion, and collagen IV expression, suggesting a potential pathological role of MBL on the kidney under diabetic conditions [140]. The adverse renal effects of MBL signalling under diabetic conditions have since been confirmed by other studies in mice with streptozotocin-induced diabetes [141–143]. One study that examined MBL levels after the induction of diabetes as well as the half-life of injected recombinant human MBL showed not only a rise in endogenous MBL levels after the induction of diabetes, but also an increase in the half-life of recombinant human MBL, indicating that the elevation in MBL with diabetes is a result of increased MBL production and decreased MBL turnover [144]. One study demonstrated a twofold increase in MBL levels in glomeruli of mice with established streptozotocin-induced diabetes compared to levels in non-diabetic controls [143], indicative of a direct effect of MBL in the diabetic kidney [143].

The clinical relevance of these experimental studies has been confirmed in clinical studies of individuals with type 1 diabetes or type 2 diabetes. A cross-sectional study of normoalbuminuric individuals with type 1 diabetes reported elevated circulating MBL compared with healthy individuals [144]; moreover, MBL levels were positively associated with urinary albumin excretion levels, even within the normal urinary albumin excretion range [145]. Another study reported higher serum MBL levels among individuals with type 1 diabetes and microalbuminuria or macroalbuminuria than in individuals with normoalbuminuria [146]. In addition, genotypes associated with high circulating MBL have been associated with the development of diabetic nephropathy and increased mortality among people with type 1 diabetes [147]. In a cohort of individuals with type 1 diabetes, those with genotypes associated with high MBL had a 50% increased risk of developing nephropathy [145] and significantly greater mortality over 10 years of follow-up than individuals with a *low-expression* MBL genotype [148]. The findings from this study contrast with those from an earlier study that found no association between 19 MBL SNPs associated with MBL concentrations and the presence of type 1 diabetes or diabetic nephropathy [149]. The reason of this discrepancy is still unknown. In a study of individuals with newly diagnosed type 1 diabetes, serum MBL measured shortly after diabetes onset was a robust predictor of incident microalbuminuria over 18 years of follow-up [150]. Additional studies support an association between MBL and diabetic nephropathy among people with type 1 diabetes [144, 149–151], including a large prospective multicentre study, which reported an association between MBL concentrations and progression of renal disease from macroalbuminuria to end-stage renal disease in individuals with type 1 diabetes [144].

Finally, in people with type 1 diabetes and renal failure who received a simultaneous pancreas–kidney transplant, preoperative serum MBL levels predicted grafts and person survival, with low MBL levels associated with improved outcomes [152]. Moreover, study of individuals with type 1 diabetes and diabetic nephropathy who underwent simultaneous pancreas–kidney transplant or kidney transplantation alone [153] found that circulating MBL normalized in individuals who had undergone successful simultaneous pancreas–kidney transplantation, and that normalization mostly occurred in those with a polymorphism in the *MBL2* gene [153]. By contrast, circulating MBL remained elevated among individuals who received a kidney transplant alone, indicating that glycaemia, and not the reversal of end-stage renal disease, is associated with decreased MBL. In support of this proposal, levels of glucose and HbA_{1c}, but not serum creatinine levels or eGFR, correlated with MBL [153].

As in type 1 diabetes, MBL is strongly predictive of worsening urinary albumin excretion and mortality among people with type 2 diabetes [154]. Several studies from the past few years have confirmed the utility of circulating MBL to predict the development of nephropathy in type 2 diabetes [155–157]. One study that assessed the association of *MBL2* polymorphisms with type 2 diabetes and diabetic nephropathy among a Northern Chinese population showed an association between GA and AA genotypes of rs1800450 with type 2 diabetes, but no association between *MBL2* polymorphisms and diabetic nephropathy [156]. Those with the GG genotype of rs1800450 and the CC genotype of rs11003125 had high serum MBL, however, and the researchers reported an association between elevated serum MBL and nephropathy [156].

These studies in people with type 1 diabetes and type 2 diabetes confirm the value of circulating MBL as a robust predictor of

diabetic nephropathy, while the same consistency has not been found for polymorphisms in the *MBL2* gene. Several of the studies have assessed the predictive value of MBL and high-sensitivity C-reactive protein (hsCRP), alone and in combination, for the development of nephropathy [144, 154]. Levels of MBL and hsCRP are not correlated, which most likely is a consequence of the strong genetic influence on circulating MBL. This lack of correlation seems to be the explanation for a stronger association with the progression of nephropathy when combining the prognostic information from the two biomarkers.

Ficolins

A few studies have examined whether ficolins, like MBL, also have a role in the development of diabetic nephropathy. In one study, deletion of the M-ficolin orthologue, B-ficolin, had no effect on the development of diabetes-induced renal damage in mice with streptozotocin-induced diabetes [158]. This finding suggests that unlike MBL, B-ficolin (and potentially M-ficolin in humans) does not have a role in the pathogenesis of nephropathy. The different outcomes associated with the deletion of B-ficolin and MBL in experimental models of diabetes might relate to differences in their specific carbohydrate-binding properties [158].

A prospective 18-year observational follow-up study examined the association between H-ficolin and the risk of nephropathy among an inception cohort of 270 individuals with newly diagnosed type 1 diabetes [159]. Following adjustment for HbA_{1c}, systolic blood pressure, smoking status, and baseline urinary albumin excretion, individuals in the highest quartile for baseline H-ficolin levels had a twofold greater risk of developing worsening urinary albumin excretion than those in the lowest quartile. Thus H-ficolin levels seem to be robustly associated with risk of progression to micro- or macroalbuminuria [159]. In a recent study circulating H-ficolin correlated not only with diabetic kidney disease, but also with mortality and cardiovascular events in individuals with type 1 diabetes [160]. So far no human studies have been published on the potential association between L-ficolin or M-ficolin and the risk of developing nephropathy.

Mannose-Binding Lectin–Associated Serine Proteases

In contrast to the substantial number of studies that have demonstrated a role for MBL in diabetic nephropathy, only one published study has investigated the role of MASPs in diabetes. The investigators compared levels of MASP-1, MASP-2, and MASP-3 in 30 children and 45 adults with type 1 diabetes with levels in individuals without diabetes [161]. Compared to age-matched controls, MASP-1 and MASP-2 levels were significantly higher among adults and children with type 1 diabetes, whereas MASP-3 did not differ between those with and without diabetes. HbA_{1c} level correlated with both MASP-1 and MASP-2, with levels of MASP-1 and MASP-2 levels decreasing as a result of improved glycaemic management. So far no studies have been published on MASP levels in type 2 diabetes.

Complement components C3, C4, and C5

In addition to the increasing body of evidence supporting a role for the lectin pathway in the development of diabetic nephropathy, several studies support a role for downstream components of the complement system – C3, C4, and C5 – in nephropathy. Some, but not all, experimental studies have reported an accumulation of complement component C3 in animal models of diabetes. In studies from the 1970s, the induction of type 1 diabetes in rats by administration of streptozotocin led to an increase in glomerular C3 levels, which was normalized by transplantation of pancreas islets [162, 163]. Furthermore, transplantation of kidneys from rats with type 1 diabetes into non-diabetic rats led to decreased expression of glomerular C3 and decreased mesangial volume in 50% of transplanted kidneys [164]. One study demonstrated an increase in glomerular MBL in mice with streptozotocin-induced diabetes, but did not find a difference in the glomerular immunofluorescence intensity of complement factors C3, C4, or C9 compared to that of non-diabetic controls; however, circulating levels of the complement activation product C3a were increased in diabetic compared to non-diabetic mice [143]. Whether the apparent disparity in levels of glomerular MBL and glomerular C3 are real or due to methodological issues in that study is not known [143]. In contrast to the study described, elevated C3 have been detected in the kidneys of two other mouse models of type 1 diabetes, the non-obese diabetic mouse [165] and the OVE26 diabetic mouse [166].

Deposition of C3 in glomeruli and glomerular capillaries has also been observed in KK mice, a model of type 2 diabetes [167]. Similarly, a study in Zucker rats, which are a hypertensive, dyslipidaemic, obese, and hyperglycaemic model of type 2 diabetes, found that a single episode of renal ischaemia was followed by a significant increase in renal mRNA encoding C3, C4, C5, C6, C8, and C9, along with notable elevations in renal mRNA encoding C3a and C5a [168].

The role of downstream complement components in nephropathy has also been assessed in clinical studies. Transcriptome and immunohistochemical analyses found a sixfold increase in glomerular C3 in kidney biopsy samples from individuals with overt diabetic kidney disease [169]. In addition, plasma levels of C3 were significantly higher in people with type 2 diabetes and macroalbuminuria than in those with normoalbuminuria [170].

The relationship between complement component C4 and diabetic nephropathy has also been described in a number of clinical studies. In a study of 64 children with type 1 diabetes, 25% of the individuals had low circulating complement C4 levels, with no association with circulating levels of complement C3 fragments in the same group [171]. Another study showed that people with type 1 diabetes and microangiopathy had lower circulating C4 than individuals with normoalbuminuria, and that C4 levels were inversely correlated with the degree of complement activation [172]. This inverse association was not confirmed, however, by another study, which might suggest that low C4 levels might be a result of the diabetes, rather than having a pathogenic role in the disease [173]. Evaluations of C4 allotypes in individuals with diabetes with or without microvascular complications have not shown consistent results [174, 175].

Membrane attack complex

A series of immunohistochemical studies using antibodies directed against the C9 component of MAC [176–178] have localized MAC to the glomerular basement membrane, tubuli, and Bowman capsule in renal tissue from individuals with type 1 diabetes [176–178]. Evaluation of renal tissue from people with varying degrees of renal function demonstrated a correlation between MAC and the magnitude of mesangial expansion among persons with type 1 diabetes. The deposition of MAC in diabetic glomeruli has been confirmed in more recent studies [139, 179]. These results are interesting, as MAC is the end-product of the complement system and the elevated MAC in type 1 diabetes seems to underline the universal activation of the complement system in diabetes ranging from MBL, over MASP and C3, to MAC.

Targeting the complement system

Under normal conditions MBL and ficolins do not bind to their receptors on cell surfaces; however, AGEs in response to hyperglycaemia generate neo-epitopes to which lectin pathway pattern-recognition molecules bind [140, 180]. In addition, increased levels of glycation in diabetes lead to glycation-induced dysfunction or inactivation of complement-regulatory proteins such as CD59, which normally prevents the deleterious effects of complement overactivation by inhibiting MAC [138, 139]. The combined effects of glycation-induced inactivation of CD59 and hyperglycaemia-induced activation of complement signalling have been proposed to increase tissue deposition of MAC, thereby activating intracellular signalling pathways, which in turn release pro-inflammatory cytokines and growth factors. Three different pathways have been proposed to lead to the late complications of diabetes: those that are dependent on the complement system and activation of MAC (for example, activation of the lectin pathway through glycation of receptor carbohydrates in addition to pathways involving CD59); those that are independent of complement (e.g. the polyol pathway); and those pathways that are triggered by either hyperglycaemia and/or MAC, such as PKC and NF-κB.

A role for the complement system in various diseases has stimulated interest in the development of antibodies, small molecules, and biologics to target this pathway. Although attempts to block complement span more than 50 years, only a few drugs have made it into clinical trials, and even fewer have passed beyond phase 1 clinical trials. Nevertheless, complement therapeutics remains an area of active interest, with new insights from molecular, genomic, and structural studies, as well as the approval and success of some complement inhibitors, such as the C5 inhibitor eculizumab, for diseases such as atypical haemolytic uraemic syndrome, encouraging further research in this field [181].

Approaches to modulate complement signalling can be categorized into five main groups:

- Those that disrupt initiation of the lectin and classical pathways by inhibiting initiating complexes, e.g. MBL-, C1q-, C1s-, or MASP-neutralizing monoclonal antibodies (mAbs); or inhibiting initiating enzymes, e.g. serine protease inhibitors (C1 inhibitor [C1INH] and nafamostat mesilate).
- Those that inhibit activating enzymes of the alternative pathway, e.g. humanized immunoglobulin G1 (lampalizumab) and small-molecule protease inhibitors.
- Those that inhibit C3 convertases and/or C3 activity, e.g. C1INH.
- Those that inhibit C5 convertases and/or C5 activity, e.g. eculizumab, coversin, C5-specific aptamers.
- Those that inhibit MAC function, e.g. soluble recombinant CD59 [181].

Only a few experimental studies have assessed the therapeutic effect of blocking complement signalling in diabetic nephropathy. One study examined the effect of thrombomodulin on the development of renal changes in a diabetic mouse model of type 1 diabetes [182]. Thrombomodulin inhibits coagulation, but also prevents complement activation via its lectin-like domain. Diabetic mice lacking thrombomodulin's lectin-like domain had increased complement activation and more severe nephropathy than diabetic wild-type mice. Inhibition of complement by administration of a low molecular weight heparin (enoxaparin) reduced albuminuria and podocyte injury in the mutant mice. *In vitro* studies demonstrated that the lectin-like domain of thrombomodulin prevented glucose-induced complement injury of podocytes, suggesting that the lectin-like domain of thrombomodulin protects against diabetic renal damage by limiting glucose-induced complement activation [182].

Two studies have examined the effects of blocking complement C3a receptors [183, 184] and/or C5a receptors [183] in Sprague–Dawley rats with streptozotocin-induced type 1 diabetes [183] and a model of type 2 diabetes, induced by exposing Sprague–Dawley rats to a high-fat diet and low-dose streptozotocin [184]. Blockade of C3a and C5a receptors in the type 1 diabetes model ameliorated endothelial-to-myofibroblast transition through the Wnt/β-catenin signalling pathway, indicative of a potential protective effect of complement blockade on renal fibrotic changes [183]. Similarly, blockade of C3a receptors in rats with type 2 diabetes improved renal morphology and function by inhibiting cytokine release and TGF-β/Smad3 signalling, again supporting a role for C3a in diabetic renal changes [184].

A study in another rat model of type 2 diabetes (Otsuka Long–Evans Tokushima Fatty Rats) demonstrated that blockade of complement component C5 with the inhibitor K-76COONa diminished the severity of albuminuria and mesangial expansion [185]. Glomerular deposition of C3 was more pronounced in untreated rats with diabetes than in animals with diabetes treated with K-76COONa, supporting a pathogenic role for C5 in diabetes-induced renal damage [185].

At present it is not fully clear which way would be the best to target the complement system in order to block the development of diabetic nephropathy. Several compounds that modify the complement system are already in clinical use for other diseases than diabetic nephropathy. The most promising of these agents should be tested for their ability to prevent or slow down the progression of diabetic nephropathy. However, for future strategies it is important to recall that the complement system has an important role in host defence and, despite the potential benefits of blocking the complement system on diabetes-induced renal damage, any approach to modulate complement signalling carries considerable risks. Individuals who are deficient in components of the lectin pathway or the classical pathway (for example, MBL, MASP-1 and MASP-2, C1 or C4) typically present with recurrent bacterial infections. Individuals with deficient classical pathway signalling can have an impaired ability to clear immune complexes, which in turn increases the risk of lupus nephritis in people with systemic lupus erythematosus [181]. Individuals who have a deficiency in a component of the alternative pathway are at increased risk of developing bacterial infections of Gram-negative origin [181]. Deficiencies in the terminal paths of the complement system increase the risk of meningococcal sepsis and/or meningitis [181]. As proposed previously, the best way to minimize the risk of iatrogenic complications is to minimally affect the physiological effects of complement signalling and to block the relevant pathway as downstream as possible. Whether the adverse effects of chronic complement inhibition, as would be required for a disease such as diabetes, are unacceptable remains to be determined.

The potential mechanisms behind the renoprotective effects of incretin drugs and sodium–glucose cotransporter 2 inhibitors

As described in detail in Chapter 44, unexpected cardio-renoprotective effects were shown in the US Food and Drug Administration (FDA)–required safety studies performed before the clinical introduction of incretin drugs and SGLT-2 inhibitors.

These two new classes of glucose-lowering drugs have markedly changed the treatment of type 2 diabetes. In addition to effectively lowering glucose, incretin drugs (glucagon-like peptide 1 [GLP-1] receptor agonists and dipeptidyl peptidase 4 [DPP-4] inhibitors) and SGLT-2 inhibitors can also reduce blood pressure, body weight, the risk of developing or worsening of diabetic kidney disease and/or cardiovascular events, and the overall risk of death [186–191].

Experimental data have identified the modulation of the innate immune system and inflammation as plausible biological mechanisms underpinning the kidney-protective effects of the drugs. In addition, these drugs may block the production of pro-inflammatory cytokines and attenuate oxidative stress [186–191].

Conclusion

Hyperglycaemia is the main driver in the development of microvascular complications in individuals with type 1 diabetes and type 2 diabetes. Accordingly, strict metabolic management is a cornerstone in the primary prevention of the microvascular complications of retinopathy, nephropathy, and neuropathy. Effective treatments of microvascular disease have been developed, in particular against retinopathy (Chapter 43) and nephropathy (Chapter 44). Although many pharmaceutical and technical interventions are available that effectively prevent or delay the development of microvascular complications in diabetes, there is still an ongoing need to develop new biomarkers and therapies for these complications.

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43 Diabetic Retinopathy

Toke Bek
Department of Ophthalmology, Aarhus University Hospital, Aarhus, Denmark
Department of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark

Key points

- Diabetic retinopathy is one of the most frequent causes of blindness worldwide.
- The pathophysiology of the disease is unknown, but the morphological lesions characterizing the disease indicate that disturbances in retinal vascular function are involved in the disease pathogenesis.
- The early stages of diabetic retinopathy are not accompanied by any subjective symptoms, but the disease can be detected by screening with inspection of the ocular fundus.
- The early changes may develop into one or both of two vision-threatening complications, proliferative diabetic retinopathy and diabetic maculopathy, each with a different epidemiology, clinical appearance, and site of origin in the retina.
- Proliferative diabetic retinopathy is primarily treated by retinal photocoagulation, and diabetic macular oedema by intravitreal angiostatic treatment.
- Countries with effective population screening and timely treatment of diabetic retinopathy have managed to reduce the incidence of low vision and blindness secondary to the disease to a negligible level.

Diabetes mellitus is a disease of the intermediary metabolism that may lead to complications in all parts of the body, including the eye [1]. The ocular complications include sudden palsies of external eye muscles resulting in diplopia that normally disappear spontaneously within a few weeks. Individuals with diabetes also have reduced motility of the pupil secondary to autonomic neuropathy, and diabetes may lead to the development of cataract at a much earlier age than in the population without diabetes [2]. However, this condition can be treated by surgery with a low complication rate.

The diabetes-related complication developing in the retina, diabetic retinopathy, is a potentially much more serious condition and constitutes one of the most frequent causes of blindness worldwide [3]. The disease is characterized by morphological lesions in the retina related to disturbances in retinal blood flow [4]. The initial signs of the disease are microaneurysms and haemorrhages in the macular area (Figure 43.1) that may progress to one or both of the two vision-threatening complications, proliferative diabetic retinopathy and diabetic maculopathy. Proliferative diabetic retinopathy is initiated by occlusion of capillaries in the retinal periphery. The consequent ischaemia and hypoxia stimulate the release of growth factors that stimulate the formation of neovascularizations proximally from the ischaemic areas. In diabetic maculopathy, the early changes progress with breakdown of the blood–retina barrier, exudation of plasma proteins, and formation of retinal oedema that may expand to include the foveal region, with a resulting destructive effect on central vision.

Nomenclature

The nomenclature of diabetic retinopathy dates back to the initial descriptions of retinopathy in people with type 1 diabetes. At this time it was important to distinguish the early changes without visual loss termed simplex, background (inside the retinal background), or non-proliferative diabetic retinopathy from proliferative diabetic retinopathy, where neovascularizations grow pre-retinally and may result in vitreous haemorrhage, tractional retinal detachment, and blindness if untreated [5]. The grading of retinopathy on this scale was supplemented with a notification of whether oedema and/or exudates were present or not in the macular area (maculopathy), since such changes can threaten central vision by mechanisms other than those related to proliferative diabetic retinopathy. The surge in the number of individuals with type 2 diabetes has increased the occurrence of diabetic maculopathy to emphasize that this is a complication in its own right.

Therefore, a present-day comprehension of diabetic retinopathy should reflect the fact that early retinopathy changes can develop into one or both of the two vision-threatening complications, diabetic maculopathy and proliferative diabetic retinopathy, with different sites of origin in the retina, different epidemiologies, and different pathophysiologies (Table 43.1).

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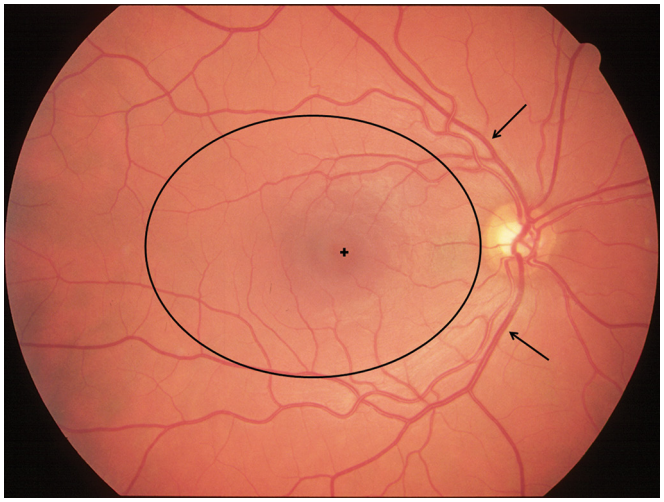

Figure 43.1 Fundus photograph of a normal eye. The retinal vascular tree branches from the optic nerve to the right. Arrows indicate the temporal vascular arcades. The ellipse delimits the macular area and the cross in the centre indicates the fovea.

Table 43.1 The nomenclature used to describe diabetic retinopathy.

Feature	Nomenclature for diabetic retinopathy	
Early changes without vision loss	Simplex retinopathy Older notation that has largely been abandoned Background retinopathy Refers to the fact that lesions are located inside the fundus background Non-proliferative diabetic retinopathy Currently used notation that is somewhat misleading as it does not indicate that these changes also precede diabetic maculopathy	
Transition towards vision-threatening retinopathy	Pre-proliferative diabetic retinopathy	Diabetic maculopathy without central involvement
Vision-threatening diabetic retinopathy	Proliferative diabetic retinopathy	Diabetic maculopathy with involvement of the area in and around the fovea

Pathophysiology

The coupling between diabetic metabolic disturbances and the development of morphological changes characterizing diabetic retinopathy is not known in detail [6]. Consequently, diabetic retinopathy has been studied from several different perspectives, and over the years a number of different hypotheses have been proposed to explain the development of the disease. One of the most productive hypotheses was the proposal of Michaelson that proliferative diabetic retinopathy results from the release of growth factors from ischaemic and hypoxic areas in the retinal periphery [7], which formed the rationale for the development of angiostatic treatment for diabetic retinopathy. Later hypotheses emphasized metabolic disturbances in the retina, such as hyperglycaemia leading to non-enzymatic glycation, shunting via aldose reductase, or activation of protein kinase C [8]. Other hypotheses have focused on specific anatomical elements as key factors in the pathogenesis of the disease, such as leucocytes, vascular pericytes, basement membranes, endothelial cells, the blood–retina barrier, neuroglia, and elements involved in neurovascular coupling [9–13]. Finally, some hypotheses have emphasized the involvement of specific reaction types such as inflammation in the development of the disease [14]. All these hypotheses can partly explain the pathophysiology of the disease, but have not individually or together been able to fully explain the development of the disease.

It is a particular feature of the retina that the inner vascular supply is devoid of autonomic nerves. This implies that retinal blood flow is autoregulated, and the vascular changes in diabetic retinopathy may be related to impairment of this autoregulation [15]. The disturbances affect both pressure autoregulation, so that retinal resistance vessels contract insufficiently when the systemic blood pressure is increased [16], and metabolic autoregulation, so that the normal dilation of retinal arterioles is reduced when the retinal metabolism increases, such as during exposure to flickering light [17]. Therefore, one of the key issues in the exploration of diabetic retinopathy is to understand the connection between diabetic metabolic dysregulation and disturbances in the regulation of retinal blood flow.

Development

Early changes with no vision loss

The initial morphological changes in diabetic retinopathy are red dots in the macular area representing capillary microaneurysms or dot haemorrhages. These two lesion types often have a similar fundoscopic appearance, presenting as small, round, reddish lesions [18]. A differentiation of microaneurysms from haemorrhages requires fluorescein angiography, where microaneurysms are hyperfluorescent and haemorrhages appear as dark spots [19]. Therefore, the idea of counting microaneurysms based on fundus photographs is conceptually meaningless. However, the clinical significance of microaneurysms and dot haemorrhages is similar, and the two lesion types should be considered together in the grading of retinopathy, just referred to as 'red dots'.

The initial lesions typically develop in the area temporal from the fovea (Figure 43.2), probably because the intraluminal pressure is particularly high in this area where the capillaries are supplied by dilated arterioles from both the upper and the lower temporal vascular arcades [20]. The presence of a few red dots implies the same risk of progression of the disease as no retinopathy, whereas the risk of progression to a vision-threatening condition increases with higher numbers of red dots [21]. Retinal haemorrhages may also assume shapes other than circular depending on the retinal anatomy at the location where the extravasated blood is distributed. One of the most striking examples is stripe-shaped haemorrhages in the retinal nerve fibre layer. Microaneurysms and haemorrhages show a highly dynamic pattern of development, with continuous new formation and resolution of lesions occurring within days to weeks [22,23]. Therefore, the progression of the disease with an increase in the total number of lesions over months to years is due to a change in this balance, where the number of newly formed lesions is higher than the number of lesions that are resolved.

The progression of diabetic retinopathy (Figure 43.3) implies an increase in the number of red dots and the occurrence of blot

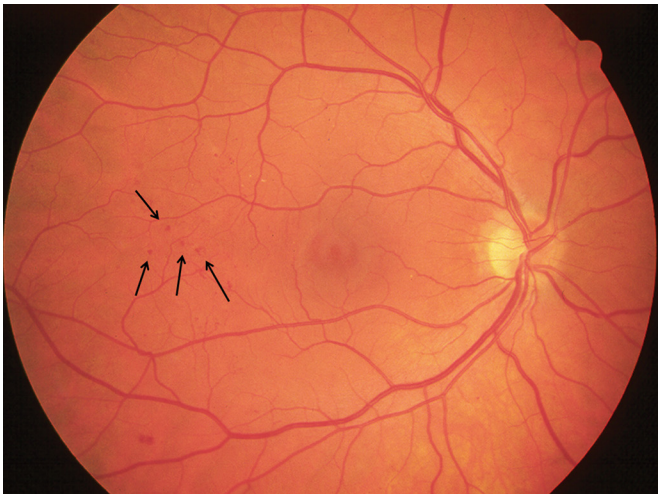

Figure 43.2 Early diabetic retinopathy with red dots (arrows) predominantly located temporally in the macular area.

Figure 43.4 Severe diabetic retinopathy with many whitish cotton wool spots developing during a period with poor metabolic management.

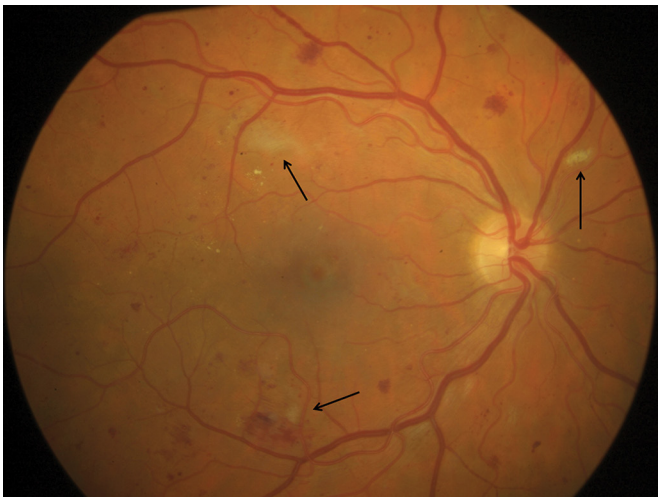

Figure 43.3 Moderate diabetic retinopathy with red dots, larger blot haemorrhages, and cotton wool spots (arrows).

haemorrhages, defined as lesions with a diameter larger than that of the vascular arcades at the crossing of the border of the optic disk [19]. Haemorrhages developing around the larger vascular arcades may indicate that impaired autoregulation has resulted in a higher than normal arterial blood pressure being transmitted to the smaller retinal vessels, with a resulting damage to the capillary system adjacent to these arcades [24].

Diabetic retinopathy may also lead to the development of cotton wool spots, which are localized, whitish lesions about the size of one-third disk diameter located at the inner surface of the retina (Figure 43.4). The lesions represent swellings of the retinal nerve fibres because the axoplasmic transport has been arrested in a focal area, with a consequent intracellular accumulation of the organelles transported to the site of the lesion [25]. Therefore, cotton wool spots are most frequently located in the arcuate areas, where the retinal nerve fibre layer is thick, and never in the foveal area or the retinal periphery, which are devoid of retinal nerve fibres. The lesions develop secondary to disturbed axoplasmic transport in the retinal nerve fibre layer, but do not point to a specific cause of this disturbance. Thus, it is erroneous to refer to the lesions *per se* as retinal infarctions, although this may be the background for the lesions in some cases. Cotton wool spots have a dynamic cycle of development and disappearance lasting weeks to months and only rarely affect visual function [26]. The development of a single cotton wool spot without any other retinopathy lesions does not imply a risk of progression of the disease, but the development of many cotton wool spots in people with other retinopathy changes (Figure 43.4) may be an indication of unstable regulation of the blood glucose levels and of imminent progression to vision-threatening diabetic retinopathy [27].

Vision-threatening diabetic retinopathy

The early retinopathy changes may progress to one or both of the two vision-threatening complications, proliferative diabetic retinopathy and diabetic maculopathy, each preceded by transitional forms.

Proliferative diabetic retinopathy

Mechanism of development

This complication is assumed to be initiated by occlusion of the capillaries in the retinal periphery. The vascular occlusion is not directly visible by inspection of the ocular fundus. However, retinal ischaemia should be suspected when the retinal fundus has a more yellowish appearance than normal and other causes such as cataract with pronounced nuclear sclerosis that absorbs short-wavelength light have been ruled out. Retinal capillary occlusion can be demonstrated by fluorescein angiography, where the lesions appear as uniform dark areas, probably due to diffuse blocking of light from the choroidal vessels caused by fluid accumulated between the photoreceptor outer segments and the pigment epithelium [28]. Fluorescein angiography may also show localized areas of capillary occlusion at earlier stages, and it has been hypothesized that these changes might be involved in the early development of the disease [29].

Occlusion of the capillary bed initiates the formation of vascular shunts from pre-existing vessels. These shunts are observed as intraretinal microvascular abnormalities (IRMAs) with a low shunting capacity [30], which are considered to be a sign of pre-proliferative retinopathy. If the capillary occlusion progresses further, the need for shunting increases further, which stimulates the formation of new vessels that grow pre-retinally. This process is stimulated by

vascular endothelial growth factor (VEGF) released from the ischaemic and hypoxic retinal tissue. Since the new vessels are connected to the high-pressure arterial vascular system, there is a risk of spontaneous ruptures of the new vessels leading to vitreous haemorrhage. The new vessels developing from the optic disk are accompanied by a higher risk of progression to result in visual loss than neovascularizations located elsewhere [31], which may be related to a higher intravascular pressure in these vessels. The clinical observation of proliferative diabetic retinopathy as a chronic progressive condition may give the impression that the disease process is irreversible. However, the fact that retinal neovascularizations may disappear a few days after anti-VEGF therapy, and even under certain conditions spontaneously [32], suggests that the natural history of these lesions is a function of changes in the retinal microcirculation and the need for arterio-venous shunting derived therefrom.

Clinical presentation

The presence of pre-proliferative changes with capillary occlusion in the retinal periphery can be suspected when one or more of the following signs (Figure 43.5) are observed [19, 33]:

- The occurrence of many blot haemorrhages temporal to the macular area. These haemorrhages may extend into the foveal region with a consequent reduction in visual acuity, which is one of the few signs of severe diabetic retinopathy that can be noticed subjectively by the individual with diabetes [34].
- IRMAs, which represent dilatations of existing vessels from the retinal microcirculation. On fluorescein angiograms, these lesions are located at the border of areas of capillary occlusion and are therefore assumed to represent shunt formations to bypass the areas of capillary occlusion.
- Many cotton wool spots, probably representing an aggravation of disturbances in blood flow and metabolism.
- Abundant reflexes from the posterior hyaloid membrane visible in younger persons where the optical media are clear. The reflections originate from the vertex of local swellings of the retina, probably reflecting localized areas of subclinical retinal oedema.
- Calibre changes of the larger retinal venules that may develop to resemble beads on a string, so-called venous beading. Under normal conditions, the diameter of retinal vessels decreases with increasing distance from the optic disk, and therefore a localized increase in the diameter can be considered to be abnormal. The background for this manifestation of diabetic retinopathy is disputed, but it may be related to metabolic acidosis or stagnant retinal blood flow.

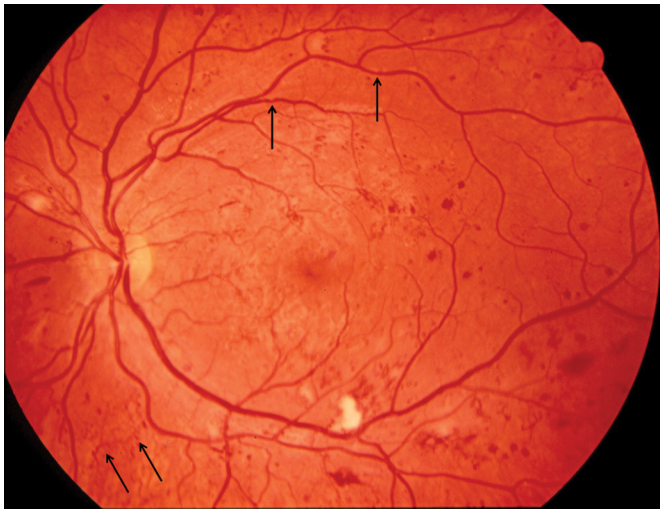

Figure 43.5 Pre-proliferative diabetic retinopathy with blot haemorrhages temporal to the macular area, cotton wool spots, venous beading (upper arrows), intra-retinal microvascular abnormality (IRMA) vessels (lower arrows), and vivid reflexes from the posterior hyaloid membrane in the macular area.

The occurrence of neovascularizations (Figure 43.6) is a pivotal event, since this prompts a need for treatment. In clinical practice, it is important to differentiate neovascularizations from shunt vessels. One of the most recently discovered measurements suitable for distinguishing the two types of vascular pathology is retinal oximetry since the oxygen saturation in the venules reflects the degree of shunting in the vessels [18, 30], but retinal oximetry is not yet a routine examination in clinical practice. The following criteria may act as a guide [35] (Table 43.2):

- Retinal neovascularization develops because of proliferation of retinal endothelial cells that penetrate the vascular wall to grow out of the vessel. However, endothelial cell proliferation may also occur inside retinal venules and contribute to the development of venous occlusions slowly enough to allow the formation of shunt vessels to bypass the site of occlusion. These shunt vessels may have the appearance of omega loops or reduplicated bypass channels (Figure 43.7). When these changes are observed, the patient will usually already have or will in the near future develop pre-retinal neovascularizations, and the condition should therefore be handled like any other case of proliferative diabetic retinopathy [36, 37].

Figure 43.6 Proliferative diabetic retinopathy with new vessels blurring the optic disk. A neovascularization at the upper temporal arcade has given rise to a pre-retinal haemorrhage extending towards the fovea.

Table 43.2 The differences between neovascularizations and shunt vessels.

Neovascularizations	Shunt vessels
Extend pre-retinally	Are located intra-retinally
Originate from larger vessels	Originate from smaller vessels
Arterial oxygen saturation	Oxygen saturation between that of arterioles and venules
May cross feeder vessel	Do not cross feeder vessel
May contain connective tissue	Do not contain connective tissue

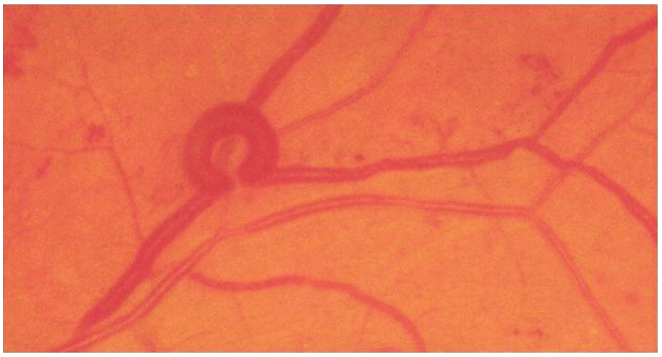

Figure 43.7 A segment of the upper vascular arcade. An omega loop represents a shunt formed to bypass an occlusion of a larger venule because of intravascular proliferation of endothelial cells. The venule extending peripheral from the loop displays changing calibre.

- Spontaneous haemorrhages emerging from neovascularizations may either be located behind the posterior hyaloid membrane and result in a localized scotoma in the visual field, or may break through to the vitreous body. This expansion of the haemorrhage results in a severe reduction in visual acuity, typically to hand movements, and a severely blurred view of the retinal fundus. If untreated, the vitreous haemorrhage may organize and together with traction from connective tissue in the new vessels the course may result in retinal detachment and total blindness.

Diabetic maculopathy

Mechanism of development

The progression of early diabetic retinopathy may result in the development of retinal oedema and/or exudates representing precipitations of plasma proteins, predominantly in the macular area. These changes are due to breakdown of the blood–retina barrier secondary to structural changes in the retinal vessels and impaired autoregulation, so that a higher than normal blood pressure is transmitted to the capillary system [38, 39]. These factors compromise the tight junctions between the vascular endothelial cells, with a consequent exudation of plasma proteins that precipitate as hard exudates.

Clinical presentation

Diabetic maculopathy is predominantly located in the macular area, but the lesions may extend to a short distance beyond the temporal vascular arcades and nasal from the optic disk. Hard exudates may develop as circular precipitations around focal points of leakage or more randomly in the macular area when the points of leakage are more distributed (Figure 43.8). Retinal oedema has been categorized according to whether it is focal or diffuse [40], which may be an indication of the severity of the condition, but the practical significance of this distinction is disputed [41].

Retinal exudates and/or oedema can progress and potentially threaten central vision. It is defined as clinically significant macular oedema when exudates and/or retinal oedema fulfil one or both of the following (Figure 43.9):

- Extend over an area larger than one disk diameter of which a part is located within one disk diameter from the fovea.
- Are located within half a disk diameter from the fovea [42].

Retinal oedema together with exudates is termed exudative maculopathy and is the commonest type of diabetic maculopathy. However, on rare occasions, macular oedema may be due to an extension of capillary occlusion from the retinal periphery to the macular area [43]. The resulting oedema is ischaemic and appears as a yellowish retinal fundus with many haemorrhages, but with no exudates. The two types of maculopathy can be differentiated by fluorescein angiography that can identify the location of respectively leakage and capillary occlusion.

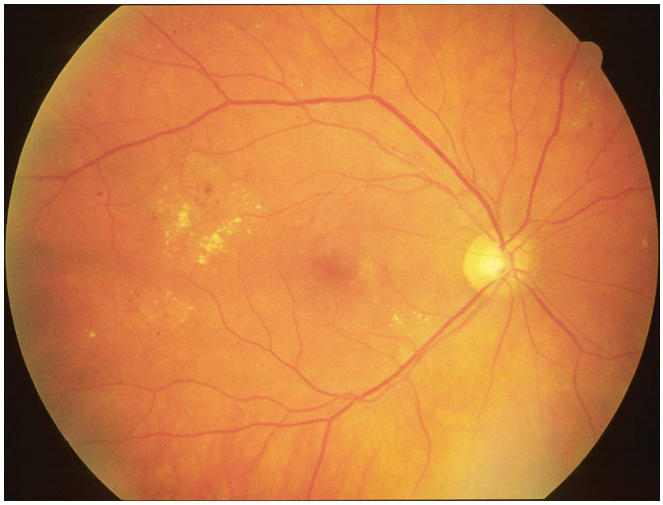

Figure 43.8 Diabetic maculopathy with exudates located temporally in the macular area.

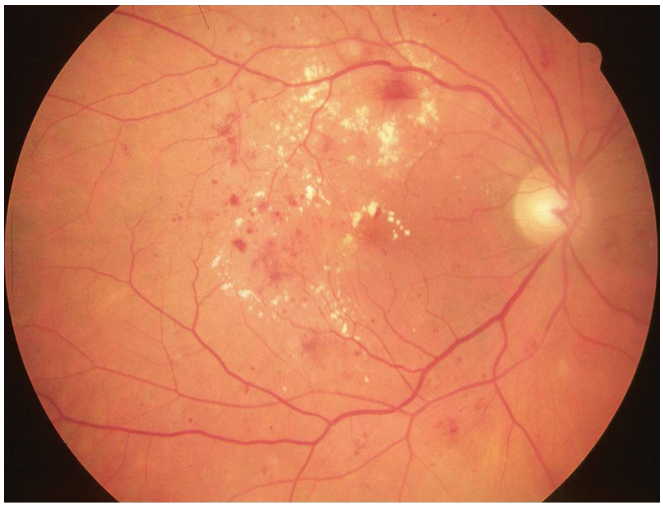

Figure 43.9 Diabetic maculopathy with clinically significant macular oedema. Exudates extend over a larger part of the macular area and involve the foveal region.

Epidemiology

Diabetes is assumed to affect ~463 million people worldwide, of whom one-third have retinopathy and one-tenth have vision-threatening retinopathy [44]. However, these estimates cover large ethnic, socioeconomic, and genetic variations. The pattern of development of diabetic retinopathy differs among the two types of diabetes and is influenced by the success of the prevention, detection, and therapy of the disease in each country. Thus, in countries with limited access to anti-diabetes medication and lack of systematic population screening, retinopathy changes may develop after a few years of diabetes duration and may be detected so late that

vision-threatening changes have developed. Therefore, the incidence and prevalence of diabetic retinopathy vary considerably, and estimates of the occurrence of the disease mostly refer to countries where data from organized population-based screening and management of diabetic retinopathy are available.

In type 1 diabetes, a few microaneurysms and/or dot haemorrhages may be present at the time of onset of the disease, but these lesions disappear so that the initial signs of diabetic retinopathy in progression appear after ~10 years' duration of diabetes [45]. The prevalence of diabetic retinopathy subsequently increases gradually until ~20 years' duration of diabetes, when almost all people with diabetes have some retinopathy [46]. The incidence of vision-threatening diabetic retinopathy gradually increases until ~25 years' duration of diabetes, after which it declines. This suggests the existence of constitutional factors affecting the risk of developing vision-threatening retinopathy within the first decades' duration of diabetes that overlie the risk of disease progression related to the cumulative exposure to metabolic dysregulation. In populations with comprehensive and organized screening and treatment programmes, half of all individuals with type 1 diabetes develop vision-threatening retinopathy, of whom two-thirds develop proliferative diabetic retinopathy and one-third develop diabetic maculopathy [47].

In type 2 diabetes, the onset of the disease is gradual and it may not be diagnosed for several years after its onset [45], so the occurrence of retinopathy in the undiagnosed population is not negligible [48]. At the time of diagnosis of type 2 diabetes, retinopathy can be observed in a considerable number of individuals, some of whom have already developed vision-threatening retinopathy [49]. After the time of diagnosis, the annual incidence of vision-threatening diabetic retinopathy is constant, and less than 10% of the individuals reach one of the treatment-requiring conditions, proliferative diabetic retinopathy and diabetic maculopathy. Since the number of people with type 2 diabetes is larger than the number of those with type 1 diabetes, the absolute number of individuals developing vision-threatening retinopathy is approximately the same in the two groups.

Prevention

The occurrence and development of diabetic retinopathy are influenced by a number of modifiable and non-modifiable risk factors. Studies of non-modifiable risk factors such as ethnicity [50], gender [51], actual age, and age at onset of diabetes [52, 53] have provided important information about the epidemiology of the disease. However, modifiable risk factors have received much more attention because of the potential for clinical intervention. Thus, the development of diabetic retinopathy correlates with average glucose levels both higher and lower than normal [54], with fluctuations in glycaemia [54], while interventions to improve glycaemic management can reduce the risk of progression of the disease in both type 1 diabetes [55] and type 2 diabetes [56]. Similarly, the development of diabetic retinopathy correlates with the systemic blood pressure [57], and a lowering of the blood pressure can reduce the progression of retinopathy in both type 2 diabetes [57] and type 1 diabetes [58]. Close monitoring of blood glucose and blood pressure can halt the progression of diabetic retinopathy and is especially relevant during pregnancy, where irregularities in metabolic regulation may have detrimental effects on the eye.

It has been suggested that the formation of hard exudates may be related to plasma cholesterol levels [43], but clinical intervention studies are lacking to document that a reduction in plasma lipids can reduce the risk of diabetic maculopathy. The development of diabetic retinopathy also depends on the type of diabetes and several studies have reported a higher frequency of retinopathy in men than in women, which may be due to men paying less attention to lifestyle [51].

The most recent evidence documents that systemic risk factors contribute differently to the development of proliferative diabetic retinopathy and diabetic maculopathy, suggesting that the overall risk of developing vision-threatening diabetic retinopathy should be calculated from the risk of reaching each of these two complications separately [54].

Screening

Diabetic retinopathy is suitable for screening because the disease fulfils the following criteria [59]:

- *The development and early progression of the disease are not detected by the individual with retinopathy*. Since diabetic retinopathy initially develops and progresses outside the foveal area, the individual will not have subjective symptoms until the late stages when damage to central vision has started. Therefore, a screening examination with inspection of the ocular fundus is needed in order to detect early retinopathy lesions before they become a threat to central vision.
- *The disease is frequent*. Diabetic retinopathy is frequent among individuals in whom diabetes has been diagnosed and therefore justifies screening for diabetic retinopathy in this population [60, 61].
- *The disease can be detected*. Diabetic retinopathy can be detected by inspection of the ocular fundus, which is achievable in all persons unless impeded by cataract or other media opacities.
- *The disease can be treated*. Studies have confirmed the beneficial effect of retinal photocoagulation, intravitreal angiostatic pharmacotherapy, and vitrectomy for the treatment of diabetic retinopathy. This implies that therapeutic benefits can follow the detection of diabetic retinopathy.
- *Screening is cost-efficient*. Health economic analyses have documented that in addition to the beneficial effects for individuals screened for diabetic retinopathy, the procedure is also highly cost-efficient for society [62].

Screening for diabetic retinopathy comprises inspection of the ocular fundus, which may be supplemented with a measurement of visual acuity in order to assess the consequences of the disease for central vision [63]. It is recommended that the fundoscopic appearance is documented by photography, which gives an overview of lesions in all parts of the fundus background, allows retinopathy lesions to be reviewed in order to obtain further opinions, and allows a detailed evaluation of changes in the morphological appearance of the disease over time. It has been a matter of debate whether screening examinations should be performed without dilatation of the pupil (non-mydriatically) in order to allow a faster and more feasible examination procedure for the patient, and the availability of cameras for imaging of the retina through small pupils has facilitated this approach. The disadvantage of this photographic approach is a reduced quality of images from the retinal periphery.

A single fundus photograph provides indirect information about depth relations in the retina, which can only be inferred from differences in focus or from the presence of overlying

structures. However, fundus photography can be supplemented with stereo fundus photography, where duplicate fundus photographs are recorded with the camera moved slightly to each side so that the light path is tangential to the left and right pupil margins. The resulting images have different disparities and when studied binocularly the grader will obtain a stereoscopic view of the retina, which can be used to diagnose macular oedema. However, the evaluation of depth relations in the retina by stereopsis is subjective, and nowadays the evaluation of macular oedema should be performed by optical coherence tomography (OCT) scanning [64].

Fundus photography should cover retinal areas where relevant retinopathy changes can be detected. This can be achieved by seven photographic fields using a 30° field of view as in the US standard [65] or by two wider-field images as in the European standard [63]. Grading of retinopathy is performed by comparing the pattern of retinopathy with a set of standard images representing the different stages of the disease, and is designed so that all levels of retinopathy have the same risk of progression from one level to the next. This semiquantitative grading method considers the type, overall severity, and location of lesions in different quadrants and in relation to the fovea, but the images contain unused information, such as the number, shape, size, detailed location, and dynamics of the lesions. In order to include this information in the evaluation, initiatives have been taken to develop computer algorithms for quantitative analysis of diabetic retinopathy lesions. This work has been challenged by the lack of gold standards for lesion detection. Hence the interpretation of findings in the retina depends on image quality, and even experienced clinicians may disagree about the identification of retinal lesions [66]. The element of pattern recognition in retinopathy grading has stimulated efforts towards developing computerized grading and decision algorithms based on artificial intelligence, and the potential of this approach is under investigation [67].

The immense task of evaluating fundus photographs obtained during population screening for diabetic retinopathy has stimulated the training and certification of non-academic graders to manage this task. The grading of diabetic retinopathy should result in answers to the following two questions:

- What is the time interval to the next screening examination?
- Should the patient be referred for further diagnostic evaluation or treatment?

The time interval to the next screening examination is generally determined by rule-based decision algorithms. On the basis of the diabetes type, diabetes duration, and retinopathy grade, a standard interval is recommended so that the disease will not progress undetected to a vision-threatening stage, even in those with the fastest disease progression [68]. However, this conservative approach implies that the individuals in whom disease progression is slow will experience superfluous examinations, because the disease has not progressed by the time of the following examination. Therefore, new algorithms are being developed with the aim of individualizing the control interval and optimizing screening by reducing the number of unnecessary examinations. These algorithms consider individual risk factors in order to prolong the control interval as much as possible while ensuring that the condition does not progress to vision-threatening retinopathy [69–71]. However, individualized control intervals may be difficult to remember for both the person with diabetes and the doctors and other personnel involved in patient care. This is further complicated if optimized retinopathy screening implies that the examinations are not synchronized with visits for metabolic regulation and screening for other late diabetes-related complications.

Screening for diabetic retinopathy is a complex challenge that involves ophthalmological, technical, and organizational elements, and should therefore be adapted to the local healthcare system in each country. The potential of such efforts has been proved in countries where screening for diabetic retinopathy has reduced the occurrence of blindness secondary to diabetic retinopathy to a negligible level [72].

Diagnosis

Diabetic retinopathy is defined and diagnosed by inspection of the ocular fundus in order to identify the typical morphological lesions that characterize the disease. Observation of the retina in red-free light may increase the contrast to improve the detection of lesions, but a detailed evaluation of the disease requires information about colour in order to distinguish red lesions from pigmentation. When diabetic retinopathy has progressed to a stage where treatment should be considered, the addition of other imaging techniques may be required.

Fluorescein angiography (Figure 43.10) is a photographic recording of retinal morphology after intravenous injection of fluorescein, where the fluorescent dye is distributed in the systemic circulation and reaches the eye. In order to detect fluorescein in the retina, an excitation filter that transmits short-wavelength light is inserted into the light path that illuminates the retina, and a barrier filter that transmits longer wavelengths is inserted in front of the photographic film. Previously, the method was used routinely for the diagnosis of diabetic retinopathy, but has to a large extent been replaced by less invasive techniques, and at present fluorescein angiography is restricted to special diagnostic cases. The method is unique for detecting leakage of fluorescein from the retinal vessels as an indication of breakdown of the blood–retina barrier [73] and capillary occlusion that appears as well-defined and uniformly black areas delimited by perfused vessels that are often leaky [43]. The method plays a particular role in the differentiation of exudative macular oedema from ischaemic macular oedema, which should be managed differently.

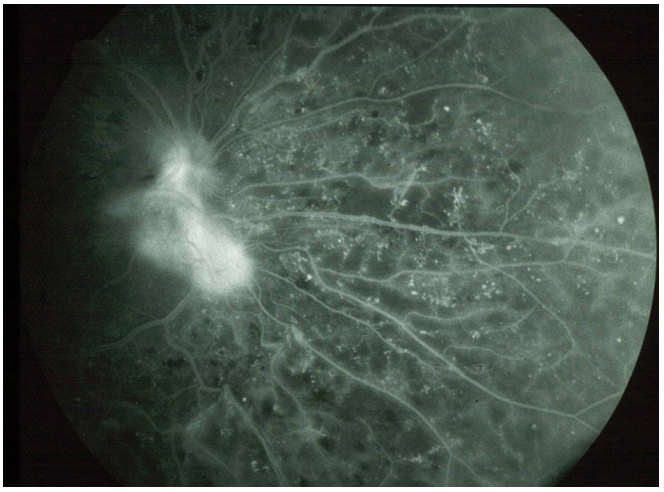

Figure 43.10 Fluorescein angiogram showing focal areas of capillary occlusion and leakage from bordering vessels. Microaneurysms are seen to fill with fluorescein. The hyperfluorescent area to the left represents a neovascularization.

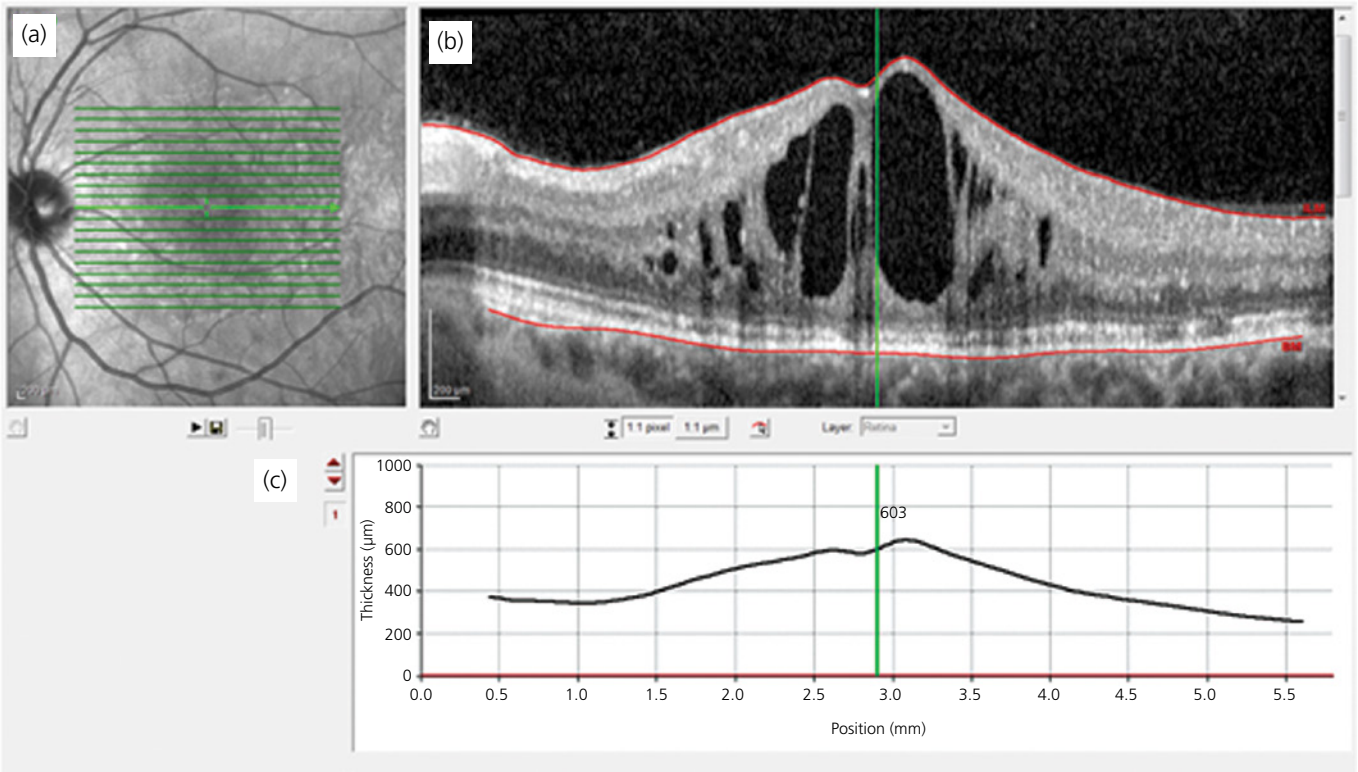

Figure 43.11 (a) Horizontal green lines represent the optical coherence tomography (OCT) scanning lines in the macular area from a person with diabetes. (b) The OCT scan through the fovea shows cystic macular oedema secondary to diabetic maculopathy. (c) The graph represents the profile of the retinal surface along the OCT scan.

OCT scanning records the latency of light pulses reflected from different retinal layers, which is translated to a measure of depth in the retina (Figure 43.11). The method can determine the depth location of individual layers in the retina with an accuracy of less than 10 µm, and is therefore suitable for detecting pathological lesions in the retina not visible by clinical inspection [74] and for quantifying retinal oedema in diabetic maculopathy [75]. This allows monitoring of the effect of treatment of retinal oedema, but the method is also suitable for differentiating diabetic macular oedema from other causes of retinal swelling, such as traction from the posterior hyaloid. At present the potential of OCT angiography for the diagnosis of diabetic retinopathy is under investigation. The technique allows the presentation of perfused vessels and therefore has potential for assessing areas of capillary occlusion [76].

Other techniques are used to study vascular changes in diabetic retinopathy, such as vessel analysis, oximetry, adaptive optics imaging, and flow measurement [77–80]. However, these techniques are research tools and do not at present have a role in daily clinical practice.

Treatment

Retinal photocoagulation

Retinal photocoagulation was the first available treatment with a documented effect on diabetic retinopathy and still has a central role in the treatment of the disease [81]. The treatment is typically applied through a contact lens, where localized laser burns with a width of 200–500 µm are applied in a grid pattern with spacing corresponding to the width of one burn. The adverse effects of the treatment are related to the destructive effects on retinal tissue. At the initiation of a treatment session, the patient will have a strong sensation of glare, which often disappears after a while when the retina adapts to the intense light exposure. During the treatment, the applications may induce a distinct feeling of pain, especially when delivered in the retinal periphery corresponding to the horizontal and the vertical meridians. However, this sensation is individual, ranging from no symptoms in some individuals to a need for retrobulbar anaesthesia in order to complete the treatment in very sensitive individuals. After the treatment, it takes a few minutes to adapt to ambient light conditions, and during the following days or weeks the patient may experience blurred vision and flashes in the visual field corresponding to the laser applications. The treatment will induce permanent shrinkage of the visual field and reduce dark adaptation, but in most cases the patient will adapt to this new situation, especially when both eyes have been treated and the brain has adapted to integrate the modified visual inputs from the two eyes.

In proliferative diabetic retinopathy, the treatment is applied outside the macular area extending to the retinal periphery, and the beneficial effect is assumed to be related to the elimination of ischaemic and hypoxic retinal tissue, with a consequent reduction in the release of the growth factors that stimulate neovascularization. The treatment typically requires 2000–3000 applications and is performed in several sessions until the intended clinical response has been obtained (Figure 43.12). The visual prognosis decreases with age and with lower visual acuity before treatment, whereas the number of laser applications necessary to halt the disease has no influence on the visual prognosis [82].

Proliferative diabetic retinopathy may lead to vitreous haemorrhage with a consequent impairment of vision. This condition can

Figure 43.12 Fundus photograph one year after panretinal photocoagulation of the case shown in Figure 43.6. The hyperpigmented laser scars extend to the retinal periphery beyond the borders of the image.

be the presenting sign of retinopathy if the patient has not been followed regularly in a screening programme, but may also occur in individuals who have received photocoagulation in whom retinal neovascularization has not regressed. Vitreous haemorrhage leads to a sudden reduction in visual acuity and therefore the patient will be referred to an ophthalmologist. If the patient has not received photocoagulation, it is important to perform ultrasound B-scan examination to rule out rhegmatogenous retinal detachment and other conditions that might indicate surgical intervention. In simple vitreous haemorrhages spontaneous resolution should be awaited for a few weeks to allow inspection and/or treatment of the retina with photocoagulation [83]. If the haemorrhage does not resolve spontaneously, the treatment of choice is vitrectomy with surgical removal of the vitreous opacities [84]. The clearing of the vitreous body may at the same time restore a clear view to the retina to allow retinal photocoagulation. The visual prognosis depends on the damage to the retina induced by the retinopathy hiding behind the opacities. Interestingly, vitrectomy has also been suggested for the treatment of diabetic maculopathy, since the replacement of the vitreous body with saline can improve diffusion and thereby facilitate the exchange of oxygen and other metabolites to the retina [70]. Retinal photocoagulation and vitrectomy will also often lead to regression of new vessels in the iris and the anterior chamber angle of the eye, but if this regression is insufficient the patient may need treatment for neovascular glaucoma.

In diabetic maculopathy, retinal photocoagulation is considered as first choice if exudates or retinal oedema are located outside the foveal area without threatening central vision [85]. The treatment is assumed to facilitate diffusion of oxygen and other nutrients from the choroid, and the elimination of metabolically active retinal tissue induces a contraction of the pathologically dilated retinal vessels [86]. It is a general misconception that focal treatment of microaneurysms is effective. Owing to the fast turnover, the lesions disappear spontaneously whether treated or not [23]. However, the treatment may in general reduce the permeability of the retinal vessels and result in regression of hard exudates that have precipitated in circles around the leaking point [87]. The treatment is applied corresponding to areas with retinal oedema, but sparing the papillomacular bundle and a zone within 500 µm from the fovea, which can often be achieved by a few hundred applications. People with reduced visual acuity may have extrafoveal fixation, and if photocoagulation is considered, care should be taken not to involve these area. In ischaemic maculopathy perifoveal capillaries may be occluded so that the foveal avascular zone is enlarged. In these cases, retinal photocoagulation may reduce central vision and is therefore not recommended.

Intravitreal angiostatic treatment

Several new approaches for intravitreal pharmacotherapy have been introduced for the treatment of diabetic retinopathy and retinal vascular diseases in general.

The introduction of intravitreal treatment with anti-VEGF medication has improved the visual prognosis of diabetic retinopathy significantly [88]. The effect of the compound is dual, with a tightening effect on the blood–retina barrier that is beneficial for diabetic macular oedema [89–91] and an angiostatic effect that can reduce neovascularization in proliferative diabetic retinopathy [92]. The advantage of the treatment is the lack of destruction of retinal tissue, but injections should often be repeated at an interval of months, with a consequent cumulation of the risk of adverse effects such as infection, glaucoma, cataract, and retinal detachment. These prospects of life-long repeated intravitreal injections are less attractive in younger people. The treatment comprises a loading phase with three injections separated by one month, followed by regular controls where the treatment can be repeated depending on the clinical response. The treatment is the first choice in those with diabetic maculopathy where the retinal oedema is mainly located in the foveal area, centrally from the zone that is accessible for retinal photocoagulation (Figure 43.13).

Diabetic macular oedema not responding to anti-VEGF treatment may in some cases benefit from intra-vitreal injection with steroid. This treatment may reduce diabetic macular oedema, which supports the hypothesis that inflammation is involved in the disease process. Because of its anti-inflammatory effect, intravitreal steroid injection is also used to treat cystoid macular oedema after cataract surgery. However, the treatment may be accompanied by adverse effects such as glaucoma and cataract, which should be considered in the treatment strategy [88, 93].

The effects of intra-vitreal pharmacotherapy with anti-VEGF compounds and steroid are often transient and should be administered repeatedly, in some cases over years. However, the transient effect of the treatment may provide a time window for the initiation of other therapies with a more permanent effect. Thus, preoperative injection of anti-VEGF compound may reduce the size of retinal neovascularizations, which in turn reduces the risk of haemorrhage during vitrectomy and panretinal photocoagulation [94].

Treatment guidelines

The advent of intra-vitreally administered compounds for treatment of diabetic retinopathy has initiated several clinical trials and implies that the recommendations for treatment are under continuous revision. However, the generally accepted algorithm for treating diabetic retinopathy is as follows [95].

Proliferative diabetic retinopathy:

- Panretinal photocoagulation, optionally preceded by intravitreal anti-VEGF compound.
- Vitrectomy if photocoagulation is insufficient or is instituted too late so that unresolving vitreous haemorrhage or retinal traction has developed. The treatment can be preceded by intra-vitreal anti-VEGF compound.

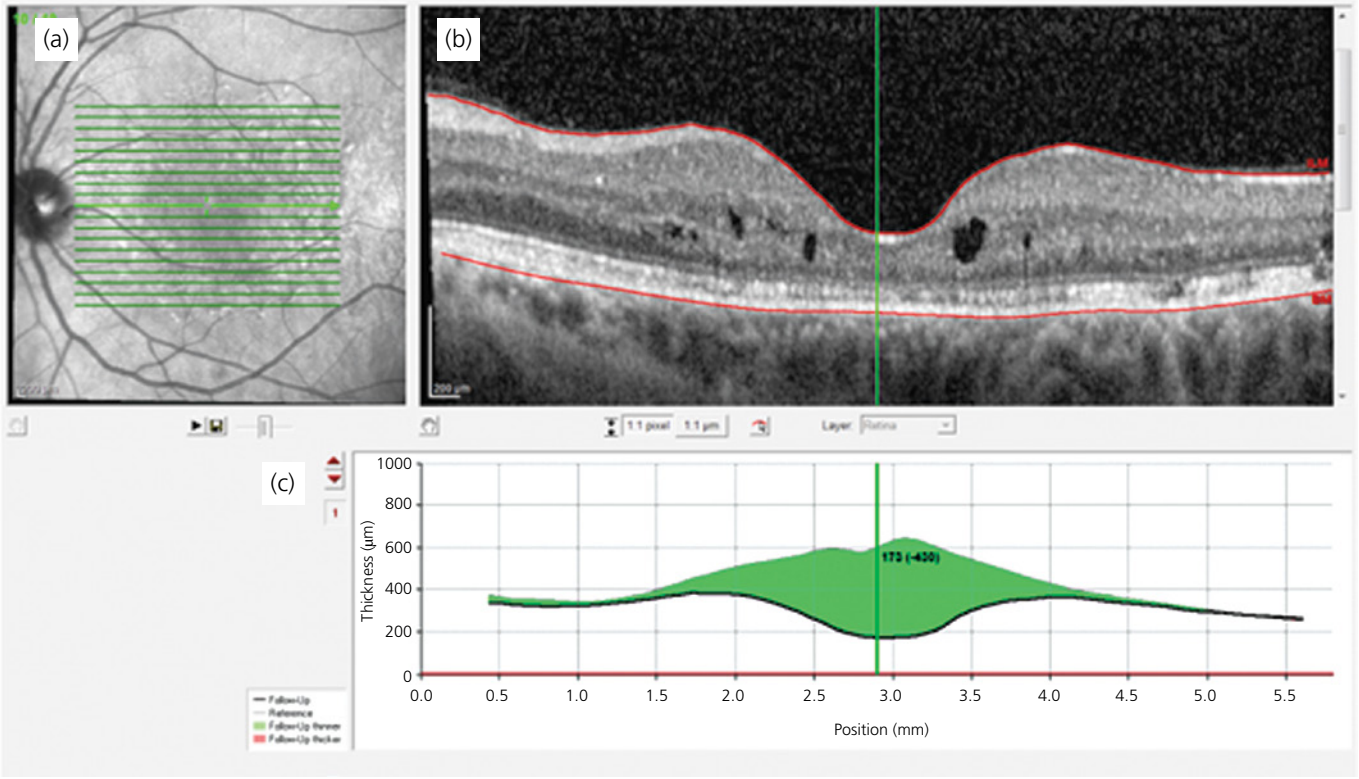

Figure 43.13 (a) Horizontal green lines represent the optical coherence tomography (OCT) scanning lines in the patient shown in Figure 43.11 and recorded three months after intravitreal injections of vascular endothelial growth factor (VEGF) inhibitor. (b) The OCT scan through the fovea shows that the retinal swelling has been reduced to a few cysts and the fovea has been restituted. (c) The graph represents the retinal profile along the OCT scan before and after treatment. The green area represents the reduction in retinal thickness along the scan.

Diabetic macular oedema:

- With central involvement or visual acuity lower than 0.67 assumed to be secondary to diabetic macular oedema, intra-vitreal anti-VEGF compound.
- Without central involvement, retinal photocoagulation, optionally supplemented with intra-vitreal anti-VEGF compound.
- Lack of effect of anti-VEGF compound and during pregnancy: intra-vitreal steroid.

The results of several clinical trials indicate that repeated injections of anti-VEGF compounds may in some cases be an alternative to photocoagulation for the treatment of proliferative diabetic retinopathy, and that vitrectomy may in some cases be beneficial for the treatment of diabetic macular oedema. However, the clinical implications of these trials are disputed, and the results have not yet been incorporated into generally accepted guidelines.

Investigation of diabetic retinopathy

During the past 50 years, immense efforts have been invested in understanding the pathophysiology of diabetic retinopathy, and several developments have significantly shifted the management of the disease during this period. In the 1960s, the beneficial effect of retinal photocoagulation was discovered by serendipity and once fluorescein angiography had been accepted by the ophthalmological community, this diagnostic method added significantly to the diagnosis and understanding of the disease. In the 1980s, vitrectomy was refined for the treatment of severe proliferative diabetic retinopathy, and systematic screening programmes for diabetic retinopathy were initiated worldwide. In the 2000s, intravitreal angiostatic treatment was introduced, based on the discovery of VEGF as a key compound involved in increasing vascular permeability and stimulating neovascularization.

However, there is still a lack of understanding of how the diabetic metabolic dysregulation triggers processes in the retina to initiate and accelerate the development of diabetic retinopathy. Vascular changes resembling early diabetic retinopathy have been induced in small rodents, and more advanced diabetic retinopathy–like changes have been generated in diabetic dogs, pigs, and monkeys. However, the full spectrum of lesions observed in human diabetic retinopathy has not been reproduced in these models, which is a major barrier for studying the pathophysiology of the disease. The lack of clear direction for the investigations has opened for numerous working hypotheses and studies of diabetic retinopathy viewed from different perspectives, depending on the interests and opinions of individual researchers rather than firm knowledge. Being a systemic disease, diabetes affects all elements of the eye, and almost any working hypothesis suggesting a change in a parameter in the eyes of people with diabetes can be confirmed. This implies that the research field of diabetic retinopathy is very open and productive, but leaves no certain cues about which directions of research will contribute to the next breakthroughs in the understanding and management of the disease. Therefore, the art of research in diabetic retinopathy will be to make the right choices for the future experimental strategy to follow.

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44 Diabetic Nephropathy

Peter Rossing[1,2] and Allan Flyvbjerg[1,2]

[1] Steno Diabetes Center Copenhagen (SDCC), Copenhagen, Denmark

[2] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Key points

- Classically, diabetic nephropathy is characterized by gradually increasing urine albumin excretion over many years, accompanied by slowing rising blood pressure and declining glomerular filtration rate (GFR).
- A small number of individuals with type 1 diabetes and about 30% of those with type 2 diabetes who develop chronic kidney disease have a progressive fall in GFR with no or minimal albuminuria. This may be a different form of kidney disease.
- Individuals with nephropathy are at greatly increased risk of other microvascular and macrovascular complications of diabetes.
- The risk of cardiovascular disease increases as albuminuria increases and independently as GFR decreases.
- Approximately 30–50% of white European individuals with diabetes will develop moderately elevated albuminuria; the prevalence is higher in other ethnicities.
- One-third of people with diabetes will progress to severely increased albuminuria and be at high risk of end-stage kidney disease (ESKD).
- Factors most closely associated with progression of nephropathy are suboptimal glucose and blood pressure management and baseline albuminuria.
- Screening for diabetic kidney disease should be done annually, by measuring the urine albumin-to-creatinine ratio and estimated GFR (eGFR).
- Optimal blood glucose and blood pressure management is key to the prevention of nephropathy.
- If moderately elevated albuminuria or greater is present, an inhibitor of the renin–angiotensin system should be commenced and titrated up to the maximum tolerated dose.
- Maintaining blood pressure at 120–130/75 mmHg, with the addition of other antihypertensive agents as necessary, will reduce the annual rate of decline of GFR from 10 to 12 to 3–5 ml/min/1.73 m^2.
- Reducing dietary protein intake to 0.8 g/kg body weight/d may slow the deterioration in kidney function.
- Aggressive management of other cardiovascular risk factors and prescription of aspirin reduce the incidence of cardiovascular events and of progression to nephropathy by ~60%.
- Sodium–glucose cotransporter 2 inhibitors slow the progression of kidney disease and reduce cardiovascular events, hospitalization for heart failure, and mortality in people with type 2 diabetes and nephropathy independent of changes in glucose.
- Kidney failure due to diabetes is the commonest single cause of entry to kidney replacement programmes worldwide; the majority of individuals have type 2 diabetes plus major comorbidities.
- People with ESKD and significant comorbidities should be offered dialysis. Fitter individuals benefit from kidney or kidney–pancreas transplantation, but need full cardiovascular assessment and, if necessary, treatment before transplantation.

Worldwide, chronic kidney disease (CKD) remains an important, common complication of diabetes. End-stage kidney disease (ESKD) is devastating to the individual and of enormous financial and social consequences to society. The proportion of individuals commencing kidney replacement therapy in 2018 because of diabetes varied enormously, ranging from 13% in China to 66% in Singapore [1]. In the USA, incidence rates of ESKD in people with diabetes increased by 50% between 1996 and 2006, but have stabilized since then, and in 2018 the rate was ~180 per million per year [1]. The incidence of ESKD in people with type 1 diabetes has remained stable or declined over the last decade, but increased in those with type 2 diabetes [2–5]. Most people with diabetes on kidney replacement therapy have type 2 diabetes.

Definitions

Diabetic nephropathy refers to the chronic condition developing over many years, characterized by gradually increasing urinary albumin excretion (UAE), blood pressure, and cardiovascular risk, falling glomerular filtration rate (GFR) and eventual ESKD. The clinical syndrome is associated with characteristic histopathological features [6]. A small proportion of individuals with type 1 diabetes [7,8], and ~50% of those with type 2 diabetes [9] with progressively declining GFR, have no or minimal albuminuria. We will refer to this clinical phenotype as non-classical diabetic nephropathy. 'Diabetic kidney disease' refers to both classical and

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non-classical diabetic nephropathy. CKD refers to kidney disease of any aetiology, including non-diabetes-related causes.

Screening for and classification of chronic kidney disease

Guidelines suggest systematic screening as part of the 'annual clinical review'. Albuminuria and GFR should be measured, allowing identification of proteinuric and non-proteinuric disease. Screening should be undertaken when the person is free from acute illness and has stable glucose levels, because many acute illnesses and acute hyperglycaemia increase albuminuria temporarily.

As albuminuria may increase in the upright posture and with exercise, measurements are best made in an early-morning urine sample; however, a spot urine sample is acceptable if there is no alternative. Both urine albumin and creatinine are measured and the albumin-to-creatinine ratio (ACR) is calculated. Because of the high day-to-day variation in UAE, if the first sample is positive further samples should be obtained, ideally within 1–3 months. At least two out of three measurements should be abnormal before a diagnosis of albuminuria is made.

Serum creatinine should be measured annually, using an accredited assay standardized to the recommended isotope dilution mass spectrometry reference method. Most laboratories calculate the estimated glomerular filtration rate (eGFR) with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation using serum creatinine, age, sex, and ethnicity, which estimates measured GFR more accurately than previous equations, particularly at higher levels of GFR [10]. The CKD-EPI equation also categorizes risk of mortality and ESKD more accurately than the previous Modification of Diet in Renal Disease (MDRD) equation in a wide range of populations, including those with diabetes [11, 12].

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Evaluation and Management of CKD advocates that final screening status should indicate both the GFR and UAE status, as in Tables 44.1 and 44.2, along with the cause of the kidney disease [13, 14]. The information can then be used as a measure of kidney prognosis (Figure 44.1).

Alternatively, estimations using cystatin C alone or with serum creatinine have been suggested to be slightly more precise [15]. There is no agreement that cystatin C–based estimates of GFR are superior to creatinine-based estimates [16, 17]. KDIGO guidelines recommend calculating cystatin-based eGFR in adults whose creatinine-based eGFR is 45–59 ml/min/1.73 m^2 without other markers of kidney disease [13]. However, we do not know that this approach improves the identification of individuals with progressive CKD compared with frequent measures of creatinine-based eGFR.

Table 44.1 Glomerular filtration rate (GFR) categories in chronic kidney disease.

GFR category	GFR (ml/min/1.73 m^2)	Description
G1	≥90	Normal or high
G2	60–89	Mildly decreased[a]
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

[a] Relative to young adult level.

Natural history and histopathology

Classical diabetic nephropathy

Gradually increasing UAE over many years is the hallmark of classical diabetic nephropathy (Figure 44.2). At presentation of type 1 diabetes, increased albuminuria may be present. As glucose levels return to normal, so does the albuminuria. In those who will never develop nephropathy UAE remains normal, except during periods of particularly marked hyperglycaemia or during acute intercurrent illness, when a transient increase in UAE may occur. In those who will develop diabetic nephropathy UAE increases gradually, with moderately elevated albuminuria usually appearing within 5–15 years of diabetes. Untreated, the mean increase in UAE is 20% per year. In people with type 1 diabetes, ~1.5–2.5% per annum develop moderately elevated albuminuria [18, 19], and 50% develop persistent moderately elevated albuminuria at some point [20, 21]. Approximately one-third with moderately elevated albuminuria progress gradually over a further 5–15 years to severely increased albuminuria, one-third will remain at moderately elevated albuminuria, and one-third will revert to normoalbuminuria [22, 23]. In the short term, reversion from moderately elevated albuminuria to normoalbuminuria appears common, one study reporting regression in 58% of participants over six years [24]. Short duration of

Table 44.2 Albuminuria categories in chronic kidney disease.

		ACR (approximate equivalent)			
Category	AER (mg/24 h)	mg/mmol	mg/g	Description	Previous terminology
A1	<30	<3	<30	Normal to mildly increased	Normal
A2	30–300	3–30	30–300	Moderately increased[a]	Microalbuminuria
A3	>300	>30	>300	Severely increased[b]	Proteinuria

ACR, urine albumin to creatinine ratio; AER, albumin excretion rate.
[a] Relative to young adult level.
[b] Including nephrotic syndrome.

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012			Persistent albuminuria categories description and range		
			A1	A2	A3
			Normal to mildly increased	Moderately increased	Severely increased
			<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (mL/min per 1.73 m²) description and range	G1	Normal or high	>90		
	G2	Mildly decreased	60–89		
	G3a	Mildly to moderately decreased	45–59		
	G3b	Moderately to severely decreased	30–44		
	G4	Severely decreased	15–29		
	G5	Kidney failure	<15		

Figure 44.1 Prognosis of chronic kidney disease (CKD) by estimated glomerular filtration rate (GFR) and albuminuria. KDIGO, Kidney Disease: Improving Global Outcomes. Source: Reproduced from Levin A, Stevens PE 2014 [14] by permission of Macmillan Publishers Ltd.

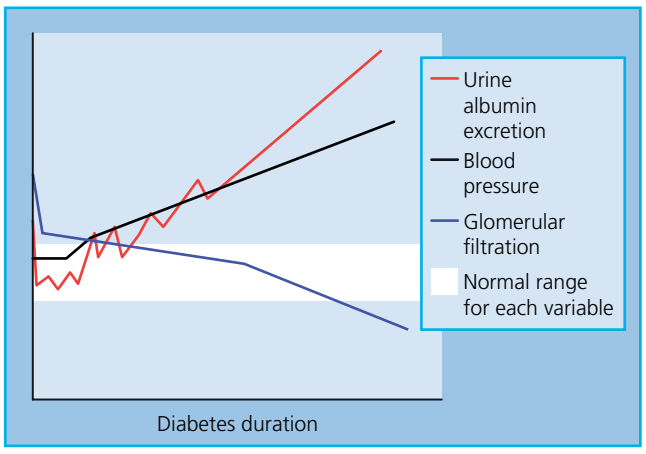

Figure 44.2 Natural history of classical diabetic nephropathy. The white bar represents the normal range for each variable.

moderately elevated albuminuria, and lower glycated haemoglobin (HbA_{1c}), systolic blood pressure, total cholesterol, and triglycerides, were all independently associated with regression. In other studies regression was rarely spontaneous but usually treatment induced [25]. The development of ESKD without albuminuria was rare in a large population-based study in people with type 1 diabetes [26]. The eventual outcome in those who regress, or who do not initially progress, remains unclear. However, they probably remain at increased risk of nephropathy compared with individuals who have never had elevated albuminuria.

Almost all people with type 1 diabetes and severely increased albuminuria eventually progress to ESKD. The use of eGFR rather than serum creatinine has unmasked a decline in eGFR within the normal range in individuals with progressive elevated albuminuria, but eGFR <60 ml/min/1.73 m^2 is rare at this stage. However, in severely increased albuminuria, the mean annual rate of decline of eGFR is 10–12 ml/min/1.73 m^2 if untreated [27].

One group has suggested that eGFR falls before the onset of albuminuria in type 1 diabetes [8]. Using serial estimates of eGFR derived from serum creatinine and cystatin C, they reported a median annual decline in eGFR of 1.5% per year in individuals with normoalbuminuria and 2.2% in those with moderately increased albuminuria. They argued that albuminuria is therefore not a good guide to diabetic nephropathy [28]. Alternative explanations are suppression of albuminuria by renin–angiotensin system (RAS) inhibitors or that kidney disease with and without albuminuria are different pathological processes, as discussed later. More recently it was highlighted that a subset of individuals with type 1 diabetes have a very fast, almost malignant decline in kidney function and should be identified with novel biomarkers [29].

The natural history of diabetic nephropathy is generally similar in type 2 diabetes. Moderately or severely increased albuminuria may be present at diagnosis and may persist in individuals who have had undiagnosed diabetes for some years. eGFR is usually >60 ml/min/1.73 m^2 at the onset of moderately elevated albuminuria, only declining to CKD stage 3 or more when severely increased albuminuria develops [30, 31].

The characteristic structural changes of classical diabetic nephropathy include basement membrane thickening, progressive mesangial expansion, alteration and loss of podocytes, and tubulointerstitial fibrosis, eventually leading to glomerulosclerosis [6].

Non-classical diabetic kidney disease

Some 7–22% of individuals with type 1 diabetes [7, 32] and 50% of those with type 2 diabetes [9, 33, 34] who develop progressive CKD do not have preceding albuminuria. Identification of people with non-diabetic kidney changes on the basis of clinical features, including the absence of diabetic retinopathy [35], is difficult. Individuals with type 2 diabetes and CKD stage 3 or more plus moderately or severely increased albuminuria are very likely to have histological features of

diabetic glomerulosclerosis, whereas those with normoalbuminuria are much more likely to have arteriosclerosis [36]. The underlying disease process in non-classical diabetic CKD probably reflects a combination of ageing, hypertension, and atherosclerotic vascular disease in addition to diabetes. Obesity, with ectopic lipid accumulation in the kidney, may also be important [37].

The rate of progression of CKD in the absence of significant albuminuria is slower than in those with albuminuria in both type 1 diabetes [8] and type 2 diabetes [38, 39]. Low eGFR and albuminuria synergistically increase the risk of ESKD.

Changing epidemiology of kidney disease in diabetes

Type 1 diabetes

Recent data suggest that per individual with type 1 diabetes, moderately and severely increased albuminuria and ESKD may be less common than previously, at least in some countries, but the number ending with ESKD is stable or increasing as the population at risk is growing with the prevalence of diabetes going up [40, 41]. Older studies suggested a lifetime risk of developing moderately elevated albuminuria of ~50%, appearing generally after 10–20 years' duration of type 1 diabetes. In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort, the cumulative incidence of persistent moderately elevated albuminuria (microalbuminuria) was 38% after 30 years in the conventional group and 25% in the intensively treated group [42]. The incidence appeared to plateau in both groups after 25–30 years. Moderately increased albuminuria developed most frequently in the second decade of diabetes in the conventional group, the incidence being blunted particularly during this time in the intensive group.

Older data suggest that the cumulative incidence of severely increased albuminuria is ~40% after 40 years' duration of type 1 diabetes. In the DCCT, after 30 years' duration, 25% of the conventional group and 9% of the intensively managed group had severely increased albuminuria [43]. Several Scandinavian studies also reported low rates of ~13% after 20–25 years' duration [44, 45]. However, in the Pittsburgh cohort, the incidence has remained relatively steady at 32% after 25 years [46].

Several European countries report a current incidence of ESKD in type 1 diabetes of 2.5–7.8% after 30 years of diabetes [47, 48]. The Pittsburgh Epidemiology of Diabetes Complications Study [49] and the WESDR cohort [50] suggested a declining incidence in those diagnosed after 1970. Survival with ESKD may also have improved.

Hence the incidence of all stages of diabetic nephropathy in type 1 diabetes may be declining, at least in some centres. However, in the UK, in the Golden Years cohort of individuals with duration of type 1 diabetes >50 years, 36% had moderately or severely increased albuminuria [51]. In a similar cohort in the USA, the prevalence of albuminuria, defined using a higher cut-off than in the UK cohort, was 13% [52]. Thus, the observed decline in incidence of nephropathy may be a delay rather than true prevention.

Type 2 diabetes

A widely varying prevalence of moderately elevated albuminuria, from 10% to 42%, has been reported. Longitudinal studies suggest that the rate of progression from normo- to moderately elevated albuminuria grade is 3–4% per annum. One older study demonstrated equivalent cumulative incidence of severely increased albuminuria in type 1 diabetes and type 2 diabetes after 25 years' duration of diabetes [53]. In the Pima, the incidence of ESKD has declined since 1990 [54]. National US survey data reported a prevalence of CKD (eGFR <60 ml/min/1.73 m^2 or UAE >30 mg/g) of 44% in the overall type 2 diabetes population and 61% in those aged ≥65 years [55]. In the UK, using a similar definition, the prevalence was 42% [56]. The increasing number of individuals with diabetes commencing kidney replacement therapy in many countries is due mainly to type 2 diabetes [1] and is accounted for in part by an increased acceptance of older, sicker individuals for treatment and improved cardiovascular survival.

Risk factors and markers for chronic kidney disease in diabetes

Many factors are associated with CKD in diabetes (Figure 44.3). Some are associated with both classical and non-classical kidney disease, and some with one but not the other phenotype [57]. Associations may be with both albuminuria and eGFR or with one measurement only. Some factors influence initial development of kidney disease and others progression of disease. Duration of diabetes is one of the strongest risk factors for diabetic nephropathy, particularly in type 1 diabetes.

Hyperglycaemia

Recent studies reinforce the importance of hyperglycaemia in the development and progression of diabetic nephropathy. An unselected Swedish cohort of individuals with type 1 diabetes was followed from diagnosis for 20–24 years [58]. No individuals with a long-term weighted mean HbA_{1c} <60 mmol/mol (7.6%) developed moderately elevated albuminuria. In contrast, 23% of those with mean HbA_{1c} >80 mmol/mol (9.5%) did so. There is a strong, graded positive association between HbA_{1c} and incident eGFR <60 ml/min/1.73 m^2, independent of other risk factors and present even in the absence of albuminuria [59]. Greater variability in HbA_{1c} is associated independently with albuminuria and diabetic nephropathy [60–62].

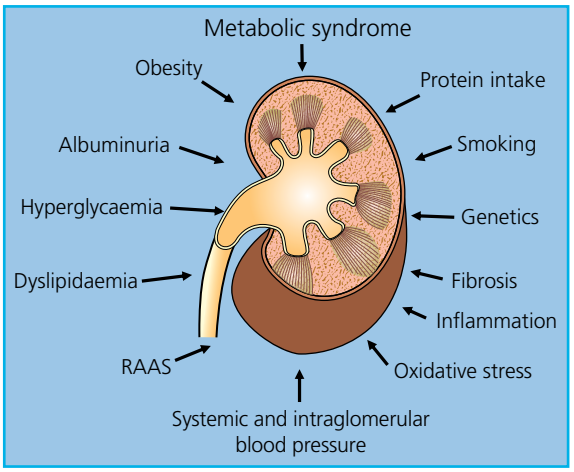

Figure 44.3 Putative promoters of progression of diabetic nephropathy. RAAS, renin–angiotensin–aldosterone system.

Blood pressure

Blood pressure is critical to the development and progression of diabetic kidney disease. The excess prevalence of hypertension in type 1 diabetes is confined to those with nephropathy [63]. In young people with moderately elevated albuminuria, changes in blood pressure are subtle, perhaps manifesting only as reduced nocturnal diastolic blood pressure dipping [64]. Once severely increased albuminuria is present, frank hypertension is present in 80% of individuals, and is almost universal in ESKD. Variability in systolic and diastolic blood pressure independently predicts the development of albuminuria in type 1 diabetes [60, 65].

In type 2 diabetes, the link between hypertension and kidney disease is less striking, because hypertension is so common. Almost all those with moderately elevated albuminuria or worse have hypertension. In people with diabetic nephropathy, variability in systolic blood pressure is independently associated with the development of ESKD [66].

Other metabolic factors

Blood lipids, including triglycerides [51,67], contribute to the development and progression of nephropathy, although the lipid phenotype alters as nephropathy progresses [68–70]. Insulin resistance increases the risk of albuminuria and a rapid decline in eGFR in type 1 diabetes [71] and of albuminuria in type 2 diabetes [72]. Uric acid predicts the development of severely increased albuminuria [73] and decline in eGFR as well as cardiovascular events [74]. Probably this association is not causal, as reduction in uric acid does not slow the decline in eGFR [75]. Individuals with type 1 diabetes or type 2 diabetes and nephropathy are more likely to have the metabolic syndrome [76–78].

Hyperfiltration

Hyperfiltration is common at the onset of type 1 diabetes and is also present in some individuals at diagnosis of type 2 diabetes. In the majority eGFR returns to normal as glucose levels return to normal, but in some individuals hyperfiltration persists. The hypothesis that individuals with persistent hyperfiltration are most at risk of subsequent diabetic nephropathy remains controversial [79–81]. Sodium–glucose cotransporter 2 (SGLT-2) inhibitors were introduced to lower glucose in type 2 diabetes, but have been demonstrated to slow the progression of kidney disease (see later). A marked effect on hyperfiltration in type 1 diabetes with SGLT-2 inhibitors was suggested to reflect lowering of intraglomerular hypertension and to support lowering of hyperfiltration as an important kidney-protective measure [82]. On the other hand, the results in type 2 diabetes were less clear [83].

Genetic factors

Genetic factors influence susceptibility to diabetic nephropathy [84, 85]. If one sibling with type 1 diabetes has nephropathy, the risk to a second sibling is increased four- to eightfold compared with siblings where neither has nephropathy [86]. The clustering of conventional cardiovascular risk factors and CVD in people with diabetic nephropathy also occurs in their parents [87, 88]. This suggests that the genetic susceptibility to nephropathy also influences the associated CVD. Multiple genes are involved, either protective or deleterious. Different loci may influence albuminuria and GFR separately [89]. Epigenetic modification may also be important [90].

Ethnicity

Albuminuria and CKD stages 4 and 5 are more common in UK Afro-Caribbean and South Asian individuals than in white European people [91, 92]. The prevalence of early CKD (defined as moderately elevated albuminuria or greater and eGFR <60 ml/min/1.73 m^2) is also higher in Latino and African American individuals than in white people [93]. Albuminuria and CKD are also more common in Pima Indians [94] and in Māoris and Pacific Islanders [95, 96] than in white Europeans. Reasons for this varying prevalence may include differing genetic influences and altered response, or poorer access, to treatments.

Type 2 diabetes developing in young people

Individuals who develop type 2 diabetes at a young age have a high prevalence of hypertension and moderately elevated albuminuria [97]. ESKD and death are particularly common in young people from ethnic minorities [98–100]. However, in some of these populations there is a high prevalence of non-diabetic kidney disease [101].

Albuminuria and estimated glomerular filtration rate

Baseline albuminuria and eGFR independently influence the development and rate of progression of CKD [102, 103]. Baseline albuminuria strongly predicts ESKD [104]. Higher levels of normoalbuminuria [105] and lower eGFR [106] predict a faster decline in eGFR. Conversely, a short-term reduction in albuminuria with intervention reduces the progression of kidney and cardiovascular complications [107, 108].

Other risk factors

Other risk factors for nephropathy include smoking predicting the development of albuminuria [103], pre-eclampsia [109], inflammatory markers [110, 111], cytokines and growth factors [112], periodontitis [113], and serum bilirubin levels [114, 115]. Obstructive sleep apnoea [116] and non-alcoholic fatty liver disease are both independently associated with diabetic nephropathy [117, 118]. Circulating levels of tumour necrosis factor-α receptor 1 are independently associated with the cumulative risk of ESKD in type 1 and type 2 diabetes [119–121].

Association of diabetic kidney disease with cardiovascular disease

The prognosis for people with diabetes and CKD is much poorer than for those without CKD. Both albuminuria and eGFR <60 ml/min/1.73 m^2 (Figure 44.4) contribute independently and synergistically to the increased all-cause and cardiovascular risk [39, 123–126].

Type 1 diabetes

In type 1 diabetes, the relative risk of premature mortality is 2–3-fold higher in moderately elevated albuminuria, 9-fold in severely increased albuminuria, and 18-fold in ESKD compared with people without diabetes [127]. Individuals with type 1 diabetes and normoalbuminuria do not have a higher risk of premature death [127, 128]. CVD is 1.2-fold more common in people with moderately increased albuminuria [129] and 10-fold higher in those with severely increased albuminuria compared with those with normoalbuminuria [130]. The cumulative incidence of CVD by the age of 40 years is 43% in people with type 1 diabetes

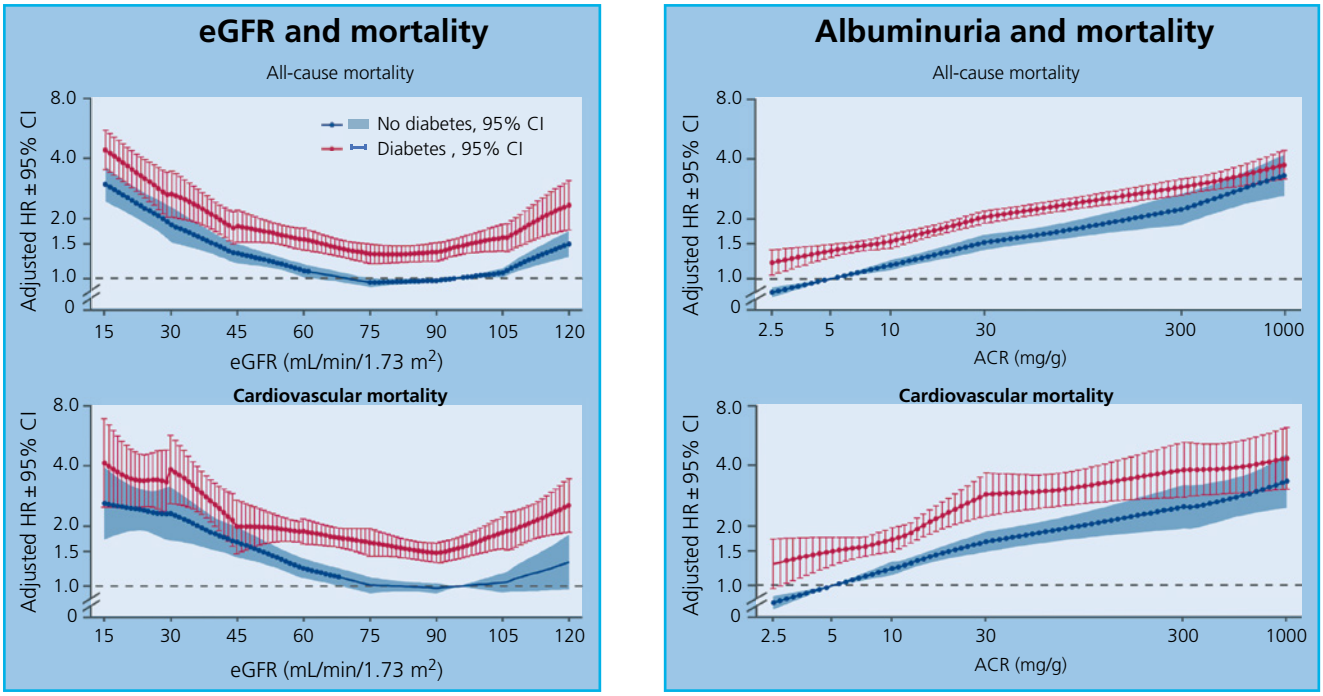

Figure 44.4 Declining estimated glomerular filtration rate (eGFR) and increasing albuminuria are associated with mortality in individuals with and without diabetes. ACR, albumin-to-creatinine ratio; CI, confidence interval; HR, hazard ratio. Source: Reproduced from Fox et al. 2012 [122] by permission of Elsevier.

and severely increased albuminuria, compared with 7% in individuals with normoalbuminuria, with a 10-fold risk of coronary heart disease and stroke. In ESKD, the risk of CVD is even higher. Median survival on kidney replacement therapy is 3.84 years [131].

Type 2 diabetes

In type 2 diabetes, CVD risk is increased 2–4-fold with moderately increased albuminuria [118, 132] and 9-fold in severely increased albuminuria [133]. Once serum creatinine is outside the normal range, cardiovascular risk increases exponentially [134]. Median survival from initiation of kidney replacement therapy is 2.16 years [131].

Microvascular complications

People with diabetic nephropathy invariably also have other microvascular complications. Significant retinopathy is almost always present in people with type 1 diabetes and moderately elevated albuminuria or more. Progression of retinopathy and development of nephropathy each increase the risk for the other, supporting the notion of a common aetiology [135]. In people with type 2 diabetes, the relationship is less clear-cut [136]. Those with classical nephropathy and progressively increasing albuminuria usually have significant retinopathy, and indeed moderately elevated albuminuria predicts the development and progression of retinopathy in type 2 diabetes [137, 138]. In those with non-classical disease, retinopathy may be absent.

Peripheral neuropathy is also more common in diabetic nephropathy, associated with both albuminuria and declining eGFR [139]. Autonomic neuropathy, reflected in loss of nocturnal blood pressure dipping, occurs frequently [140, 141] and predicts kidney function decline [142].

Investigation of kidney disease in diabetes

Excluding other treatable causes of kidney disease

It is uncommon to find a specific treatable cause of CKD if the natural history is classical. However, if there is doubt, ultrasound of the kidney tract, measurement of autoantibodies and immunoglobulins, and kidney biopsy may help.

Monitoring kidney disease

Once UAE is abnormal, the ACR should be measured every 3 months and eGFR 3–6 monthly, depending on the stage of CKD. There is a linear relationship with time and eGFR, which is useful in assessing changes in response to therapy and in predicting when an individual will reach ESKD.

Prevention and management of diabetic kidney disease

Prevention of kidney disease is crucial. Although much can be done to slow progression, it may not be possible to avoid ESKD. The risk of developing diabetic nephropathy is particularly reduced by optimizing blood glucose and blood pressure management. A guideline on management of diabetes in CKD from KDIGO emphasizes management of cardiorenal risk factors that include lifestyle factors (diet, exercise, and smoking cessation), glucose, blood pressure, and lipids, including blockade of the renin–angiotensin–aldosterone system and in type 2 diabetes SGLT-2 inhibition (Figure 44.5) [143].

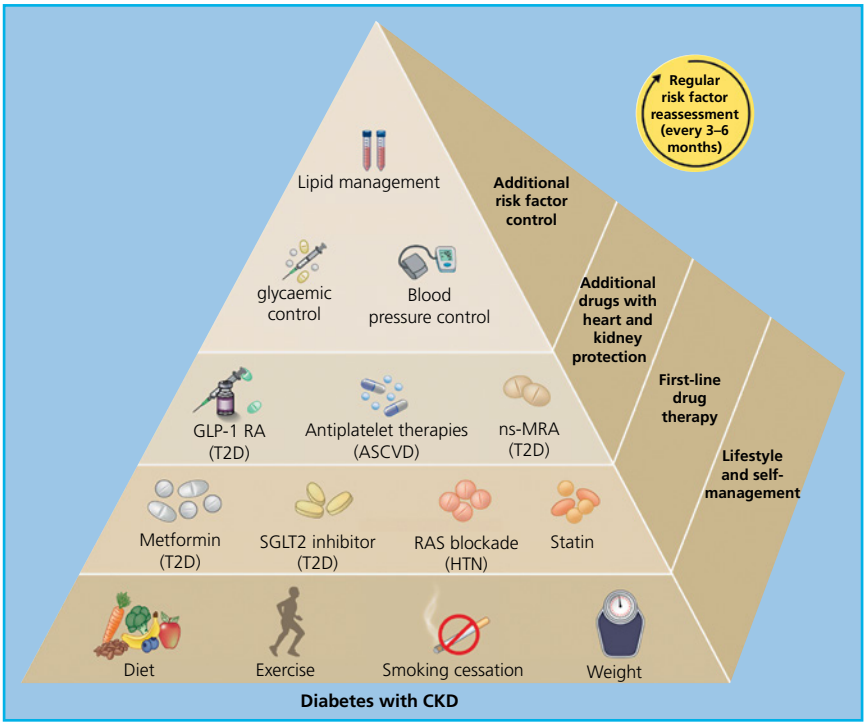

Figure 44.5 Individuals with diabetes and chronic kidney disease (CKD) should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease. GLP-1 RA, glucagon-like peptide-1 receptor agonist; T2D, type 2 diabetes; ASCVD, atherosclerotic cardiovascular disease; ns-MRA, non-steroidal mineralocorticoid receptor antagonist; RAS, renin–angiotensin system; HTN, hypertension; SGLT-2, sodium–glucose cotransporter 2. Source: Reproduced by permission from KDIGO 2022 [143].

Glucose management

Glucose management in type 1 diabetes

Among the participants in the DCCT who initially had normoalbuminuria, the relative risk reduction for development of moderately elevated albuminuria was 39% and for grade A3 54% in those allocated to the intensively treated group compared with those in the conventionally managed group over the 6.5-year study [144]. Mean achieved HbA_{1c} was 52 mmol/mol (7.0%) and 76 mmol/mol (9.1%), respectively. There is no HbA_{1c} threshold below which risk is not reduced [145].

In the open follow-up of the DCCT cohort, HbA_{1c} in the previously intensively and conventionally managed groups became similar, ~64 mmol/mol (8.0%). Despite this, the incidence of moderately and severely increased albuminuria grades [146], eGFR <60 ml/min/1.73 m^2, and ESKD [147] was significantly reduced in those who had previously received intensive management, as summarized in Table 44.3. These results are supported by an observational study of individuals with type 1 diabetes and CKD stages 1–3 with severely increased albuminuria at baseline [148]. The cumulative risk of ESKD after 15 years was significantly lower in those whose HbA_{1c} improved compared with those whose HbA_{1c} remained stable or deteriorated. Hence improving glucose management significantly reduces the risk of development and progression of all stages of diabetic nephropathy in type 1 diabetes. The beneficial effects extend far beyond the actual period of optimal glucose management, a phenomenon termed 'metabolic memory'. In highly selected individuals undergoing serial kidney biopsies after successful pancreas transplantation, kidney structural changes regressed after 10 but not 5 years [149]. Thus, prolonged periods of 'normoglycaemia' are necessary to reverse kidney structural changes. It has been suggested that not only mean glycaemic level as reflected by HbA_{1c} but also time in target glycaemic range is important for the development of renal complications [150]. In a small study insulin pump therapy was associated with less variability compared to multiple daily insulin injections, and the reduced variability and improved time in range contributed to a decline in albuminuria in type 1 diabetes with increased albuminuria, beyond any change in HbA_{1c} [151].

Table 44.3 Kidney benefits of intensive insulin therapy demonstrated by the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Cohort.

Variable	Duration of observation (years)	Conventional insulin therapy	Intensive insulin therapy
Moderately elevated albuminuria	8	15.8%	6.8%
Severely increased albuminuria	8	9.4%	1.4%
eGFR <60 ml/min/1.73 m^2	22	46 (*n*)	24 (*n*)
ESKD	22	16 (*n*)	8 (*n*)

eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; *n*, number. Source: Data from Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group 2003 [146], de Boer et al. 2011 [147].

Glucose management in type 2 diabetes

In the UK Prospective Diabetes Study (UKPDS), although the mean achieved HbA_{1c} in the intensively managed group was 53 mmol/mol (7.0%) compared with 63 mmol/mol (7.9%) in the less strictly managed group, there was a reduction in the relative risk of developing moderately or severely increased albuminuria of 30% after 9–12 years [152]. No threshold of HbA_{1c} and risk

was observed, suggesting that the lower the HbA_{1c}, the lower is the risk of nephropathy [153]. In the open follow-up of the UKPDS cohort, HbA_{1c} was similar in the previously intensively and conventionally managed groups after one year [154]. Despite this, microvascular risk remained lower, confirming the 'metabolic memory' seen in the DCCT/EDIC study. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study, the HbA_{1c} achieved in the intensively managed group was 48 mmol/mol (6.5%), compared with 56 mmol/mol (7.3%) in the standard care group [155]. In the intensive group there was a 9% relative risk reduction in new-onset moderately elevated albuminuria, a 30% reduction in the development of severely increased albuminuria, and a 65% reduction in ESKD over five years [156]. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study also demonstrated significant reductions in new-onset moderately and severely increased albuminuria and in ESKD with intensive glucose management [157]. Progression of albuminuria was reduced and regression increased. However, in those with CKD at baseline, the risk of all-cause and cardiovascular mortality was significantly increased in the intensive glucose management group [158]. Hence the kidney benefits of extremely tight glucose management are outweighed by the excess mortality. A less tight HbA_{1c} target in individuals with type 2 diabetes and duration >10 years seems sensible.

Glucose management in end-stage kidney disease

Most [159–161] but not all [162] observational studies have demonstrated increasing all-cause and cardiovascular mortality with increasing HbA_{1c} in people with diabetes on kidney replacement therapy. Some also showed a U-shaped relationship, with mortality increasing at low HbA_{1c} levels [159, 163, 164]. However, there have been no studies that demonstrated improved survival by improving glucose regulation.

Glucose-lowering medications and organ protection

Sodium–glucose cotransporter 2 inhibitors

For 20 years RAS blockade was the only treatment for diabetic nephropathy. After many unsuccessful attempts at developing new therapies, the first, and so far most marked, success has been with SGLT-2 inhibitors. When initially tested for safety in cardiovascular outcome trials, empagliflozin did not only show a benefit on the primary endpoint major adverse cardiovascular events [165], a significant benefit on hospitalization for heart failure was also observed. In addition, a reduction in incident or worsening nephropathy occurred (hazard ratio [HR] 0.61; 95% confidence interval [CI] 0.53 to 0.70) [166]. These findings were confirmed in cardiovascular outcome trials with canagliflozin and dapagliflozin. The first study with hard renal endpoints (ESKD, significant loss of renal function) as primary endpoint using an SGLT-2 inhibitor was Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE), which showed a major benefit on renal outcome but also on heart failure and major adverse cardiovascular events in people with type 2 diabetes, urine albumin creatine ratio >300 mg/g, and eGFR 30–90 ml/min/1.73 m^2 [167]. The primary outcome was a composite of ESKD, a doubling of the serum creatinine level, or death from renal or cardiovascular causes. The study was stopped early showing a benefit of canagliflozin with HR 0.70 (95% CI 0.59 to 0.82). These data were confirmed and extended by the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) study that included people with CKD with or without diabetes [168] (Figure 44.6).

Whereas SGLT-2 inhibitors were introduced to treat hyperglycaemia, they also provide organ protection in diabetes with eGFR <45 ml/min/1.73 m^2 where there is no effect on blood glucose, and in persons without diabetes with heart failure and/or CKD. The explanation for the renal and cardiac benefits is not clear, but it may

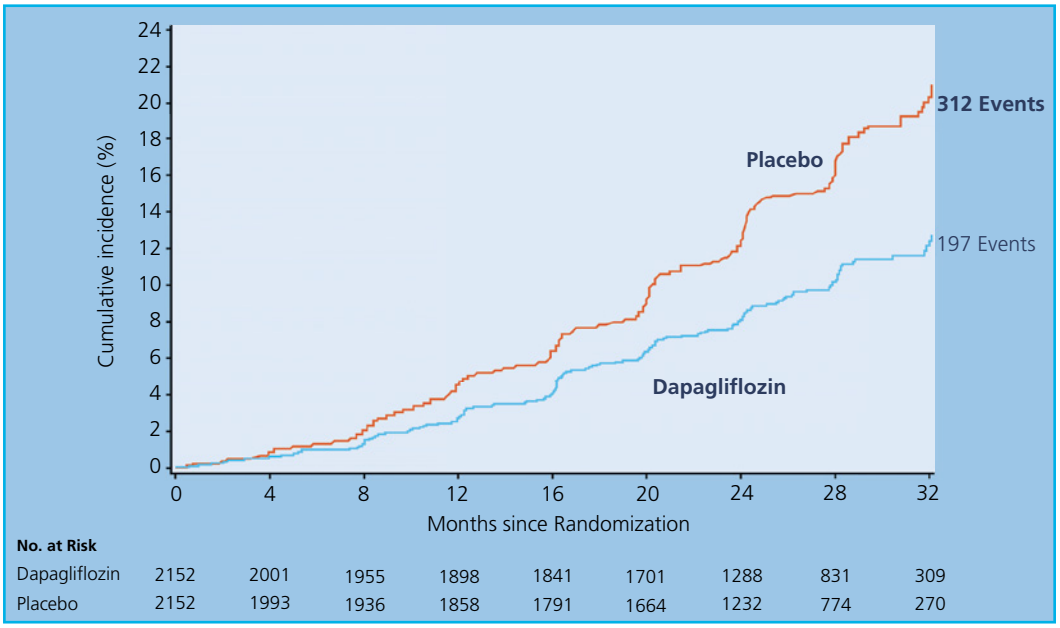

Figure 44.6 Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD): sodium–glucose cotransporter 2 (SGLT-2) inhibitor dapagliflozin or placebo in chronic kidney disease with or without type 2 diabetes. Primary outcome: sustained ≥50% estimated glomerular filtration rate (eGFR) decline, end-stage kidney disease, renal or cardiovascular death. Hazard ratio 0.61 (95% confidence interval 0.51 to 0.72), $p < 0.00001$, number needed to treat (NNT) = 19. Source: Modified from Heerspink et al. 2020 [168].

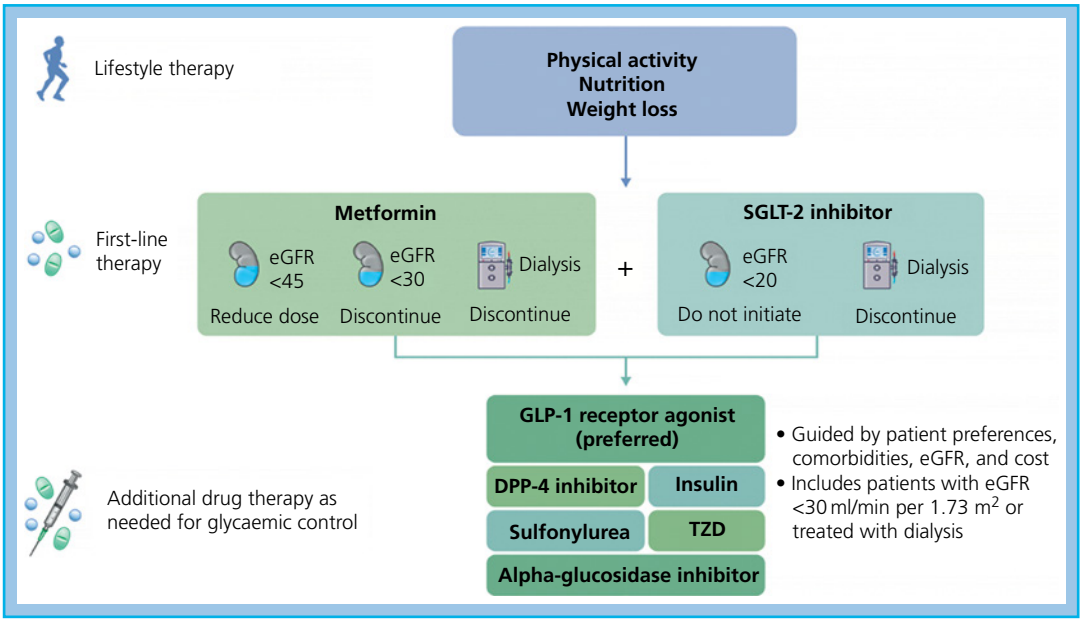

Figure 44.7 Anti-diabetes therapies in people with diabetes and chronic kidney disease. DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1; SGLT-2, sodium–glucose cotransporter 2; TZD, thiazolidinedione. Source: Reproduced by permission from KDIGO 2022 [143].

involve effects on intraglomerular pressure, hypoxia, blood pressure, obesity, and metabolic effects [169]. There are no studies in diabetic nephropathy in type 1 diabetes; the benefit may be as in type 2 diabetes, but the risk of normoglycaemic diabetic ketoacidosis is increased. In people with type 2 diabetes and CKD, metformin is recommended as the first glucose-lowering agent after lifestyle intervention, as in others with type 2 diabetes, and then SGLT-2 inhibitors are recommended independent of HbA_{1c} for their organ-protective effect [143, 170] (Figure 44.7).

Glucagon-like peptide 1 receptor agonists

For some long-acting glucagon-like peptide 1 receptor agonists (GLP-1RAs; liraglutide, semaglutide, and dulaglutide), the cardiovascular outcome trials in type 2 diabetes demonstrated cardiovascular benefits in people with pre-existing atherosclerotic CVD [170]. The benefit on CVD outcomes was also demonstrated in CKD populations, and thus GLP-1RAs are recommended in the treatment of type 2 diabetes with diabetic nephropathy when metformin and SGLT-2 inhibition are not sufficient to obtain optimal glucose regulation (Figure 44.7). Studies also demonstrated positive kidney effects as secondary endpoints, mostly driven by reductions in albuminuria, but also some potential effects on eGFR. A kidney benefit was supported by the AWARD 7 study with dulaglutide in type 2 diabetes with CKD, although the primary endpoint was glycaemia [171]. The FLOW study (NCT03819153) will determine if there are benefits on hard renal outcomes in addition to cardiovascular benefits with semaglutide.

Blood pressure management

Rigorous blood pressure management improves the prognosis in diabetic nephropathy dramatically. Conservative estimates suggest that optimal blood pressure management doubles the time taken from first appearance of severely increased albuminuria to need for kidney replacement therapy from a mean of 9 to 18 years. Improved management in moderately elevated albuminuria may prevent progression and promote regression of normoalbuminuria. Blood pressure and glucose-lowering effects are independent of one another, but have synergistic effects [172, 173]. In contrast to glucose 'metabolic memory', the benefits of blood pressure reduction are lost rapidly when control deteriorates [174].

Type 1 diabetes

RAS inhibitors do not prevent moderately elevated albuminuria in normotensive people with type 1 diabetes [175–177]. There is also no evidence that treating hypertension in type 1 diabetes and normoalbuminuria prevents the progression of albuminuria and decline in kidney function. However, it seems highly likely.

Once moderately or severely increased albuminuria is present, inhibition of the RAS is the backbone of therapy, because it reduces intraglomerular pressure. A meta-analysis summarized the effects of angiotensin-converting enzyme (ACE) inhibitors in people with type 1 diabetes and moderately elevated albuminuria [178]. The odds ratio for progression to severely increased albuminuria was reduced by ACE inhibition to 0.35, and for regression to normoalbuminuria it increased to 3.07, compared with placebo treatment. After two years of treatment, the mean reduction in UAE was 50% with ACE inhibition and was greatest in those with highest baseline levels. However, the response to treatment plateaued with time, suggesting that treatment delays, rather than prevents, progression.

Addition of an ACE inhibitor to non-ACE inhibitor antihypertensive therapy reduced the risk of a doubling of the serum creatinine by 48% and the composite endpoint of death, need for dialysis, or kidney transplantation by 50% in people with type 1 diabetes and with severely increased albuminuria and hypertension [179]. Both benefits were independent of blood pressure. In short-term studies, the effects of angiotensin receptor blockers (ARBs) on blood pressure and UAE were similar to those of ACE inhibitors in type 1 diabetes and severely increased albuminuria [180].

For a similar reduction in blood pressure, there is a greater reduction in protein excretion using ACE inhibitors compared with other classes of antihypertensive agents [181]. This may be beneficial, as the passage of protein across the glomerular filtration

barrier may accelerate the progression of nephropathy [182]. Animal data show that this is due to preferential reduction in intraglomerular pressure with ACE inhibitors [183]. An effect on the filtration barrier has also been suggested [184].

RAS inhibitors should be offered to all individuals with type 1 diabetes and albuminuria, regardless of blood pressure. The dose should be titrated up to the maximum recommended or tolerated, to maximize the antiproteinuric effect. If blood pressure remains >125/75 mmHg on a maximum dose of RAS inhibitors, antihypertensive therapy should be intensified. Lower blood pressure reduces the rate of decline of GFR from 10 to 12 ml/min/year untreated to <5 ml/min/year [185]. Regression from severely to moderately increased albuminuria can be achieved, with the fall in GFR reduced to <1 ml/min/year [186]. The choice of agent should be made on an individual basis, as there is no evidence in type 1 diabetes that any one add-on agent is better than any other. Often multiple agents are needed in CKD stage 3 and beyond.

Type 2 diabetes

Optimizing hypertension management reduces the risk of developing moderately or severely increased albuminuria [187–190]. There may be a particular benefit of RAS inhibition in prevention of nephropathy [191–193], but lowering blood pressure sufficiently is the key. Achieved blood pressure in these studies was generally ~140/80 mmHg, but most guidelines now suggest a blood pressure target of 130/80 mmHg in type 2 diabetes.

As with type 1 diabetes, there is good evidence in type 2 diabetes that inhibition of the RAS should be the backbone of therapy if albuminuria is elevated. RAS blockade reduces the progression of moderately elevated albuminuria to severely increased albuminuria [188, 194] and increases regression to normoalbuminuria [194]. The benefits are at least partly independent of blood pressure lowering. In more advanced diabetic nephropathy, RAS inhibition with ARBs reduces progression, defined as doubling of serum creatinine, ESKD, or death [195, 196]. Hence people with type 2 diabetes and moderately or severely increased albuminuria should be prescribed a RAS inhibitor, titrated to the maximum tolerated dose [197]. Hyperkalaemia is common in individuals with type 2 diabetes and nephropathy taking an ARB and is associated with increased risk of kidney failure [198]. General steps to lower potassium such as dietary advice, diuretics, consideration of potassium-increasing medication, dietary supplements, or potassium binders should be considered before stopping RAS blockade [143]. Introduction of a RAS inhibitor often leads to an acute decline in GFR, which then stabilizes. Individuals with the greatest initial fall in GFR have the slowest subsequent decline in kidney function [199].

Most people with type 2 diabetes and albuminuria will require additional antihypertensive therapy. The choice of additional agents should be made on an individual basis, with diuretics and calcium channel blockers often being appropriate. In resistant hypertension with preserved renal function, mineralocorticoid receptor antagonists (MRAs) may be useful [200].

In the UKPDS, there was no blood pressure level below which risk of developing moderately elevated albuminuria or beyond increased; that is, no 'J-shape' [201]. The ADVANCE study explored the effects of reduction of blood pressure below the currently recommended targets of 130/80 mmHg in individuals with normal or moderately increased albuminuria and 125/75 mmHg in those with severely increased albuminuria [202]. Over four years, the risk of kidney events was reduced by 21%, mainly because of reduced risk of developing moderately or severely elevated albuminuria. However, an achieved systolic blood pressure below 120–130 mmHg was associated with increased mortality and ESKD [203]. Therefore, extremely tight blood pressure should be avoided.

Dual blockade of the renin–angiotensin system

Addition of an ARB to an ACE inhibitor [204, 205] or of the direct renin inhibitor aliskiren to an ARB reduces blood pressure and albuminuria more than each agent individually. However, in the longer term, dual blockade increases the risk of hyperkalaemia, hypotension, and acute, irreversible kidney failure [206–209]. Hence dual blockade is not recommended.

Mineralocorticoid receptor antagonism

Prevention of diabetic nephropathy was attempted with spironolactone in the PRIORITY trial including people with type 2 diabetes and normoalbuminuria. High risk for progression to CKD/moderately elevated albuminuria was identified with a urinary proteomic-based risk score (CKD-273). High-risk individuals were randomized to spironolactone or placebo, and although the biomarker predicted progression of kidney disease, spironolactone did not reduce progression compared to placebo over three years [210].

Short-term studies in established diabetic nephropathy revealed ~30% reduction in albuminuria with the steroidal MRAs spironolactone or eplerenone [211]. Preventing overactivation of the mineralocorticoid receptor reduces inflammation and fibrosis, but due to potassium problems diabetes with kidney disease became a contraindication for these agents. Non-steroidal MRAs have been developed and may cause fewer potassium issues. The non-steroidal MRAs esaxerenone and finerenone reduced moderately elevated albuminuria in type 2 diabetes in short-term studies [212, 213]. The FIDELIO-DKD study tested finerenone and included 5734 participants with CKD and type 2 diabetes (urine ACR ≥30–≤5000 mg/g, eGFR ≥25–<75 ml/min/1.73 m^2) and the primary endpoint (kidney failure, sustained decrease of eGFR ≥40%, or kidney death) was reduced with HR 0.82 (95% CI 0.73 to 0.93, p = 0.001). The key secondary outcome (cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure) was also reduced (HR 0.86; 95% CI 0.75 to 0.99; p = 0.03). The incidence of hyperkalaemia-related treatment discontinuation was higher with finerenone than placebo (2.3% and 0.9%, respectively) [214]. FIGARO-DKD support the findings from FIDELIO-DKD, but in type 2 diabetes with less advanced CKD, and has CVD as a primary outcome [215].

Sodium intake

Short-term dietary sodium restriction (target sodium intake 50 mmol Na^+ per day), added to RAS blockade, reduces albuminuria [216]. The treatment effects of ARB are greater in individuals with lower rather than higher dietary sodium intake [217]. Hence dietary counselling to reduce sodium intake is essential and an intake of <2 g of sodium per day (or <90 mmol of sodium per day, or <5 g of sodium chloride per day) is recommended [143].

Non-classical diabetic kidney disease

There is no specific evidence for the use of RAS inhibition in individuals without albuminuria. However, optimizing blood pressure remains crucial to slow progression. Ongoing studies are investigating the effect of the SGLT-2 inhibitor empagliflozin on CKD, including low eGFR (20–45 ml/min/1.73 m^2) but normal UAE [218].

Endothelin receptor antagonists

Atrasentan is an endothelin receptor A antagonist that lowers proteinuria without significant oedema [219]. Previously oedema had been a concern with this class of agents [220]. The Study Of diabetic Nephropathy with AtRasentan (SONAR) study tested atrasentan in people with type 2 diabetes and severely increased albuminuria, with progression of kidney disease, ESKD, and mortality as the primary outcome [221]. Although stopped early for concern of futility, the study eventually showed a kidney benefit of the same magnitude as with SGLT inhibitors, but without effect on major adverse cardiovascular events and with a tendency to increased risk of heart failure. The primary endpoint was a composite of doubling of serum creatinine (sustained for ≥30 days) or ESKD (eGFR <15 ml/min per 1.73 m^2 sustained for ≥90 days, chronic dialysis for ≥90 days, kidney transplantation, or death from kidney failure). The HR for atrasentan compared to placebo was 0.65 (95% CI 0.49 to 0.88; p = 0.0047). The mode of action may relate to an effect on inflammation, but also an effect on podocytes and endothelium and glycocalyx has been proposed from experimental data [222].

Low-protein diet

A meta-analysis concluded that such a diet significantly improves GFR but not albuminuria, across all subtypes of diabetes and stages of nephropathy [223]. A randomized trial of 82 people with type 1 diabetes and severely increased proteinuria and progressive loss of kidney function demonstrated reduced mortality and ESKD (relative risk 0.23; 95% CI 0.07 to 0.72) for individuals assigned to a low-protein diet targeting 0.8 g protein/kg body weight/d compared to usual diet [224]. Protein intake should not be restricted to less than 0.7 g protein/kg body weight/d because of concerns about malnutrition in ESKD. In line with recommendations for the general population, a protein intake of 0.8 g protein/kg body weight/d is recommended for people with diabetes and CKD, except for those on peritoneal dialysis where a higher intake (1.0–1.2 g protein/kg body weight/d) is recommended [143].

Lipids

Lipid-lowering medications are recommended to reduce the risk for CVD, but there is some evidence that lipid-lowering agents are beneficial to the kidney. In a *post hoc* analysis of the Collaborative Atorvastatin Diabetes Study, the rate of decline of eGFR was significantly less in those individuals taking atorvastatin 10 mg daily compared with placebo. Fibrates also reduce albuminuria, although they reversibly increase serum creatinine [225].

Cardiovascular risk: other factors

Smoking increases the likelihood of developing diabetic nephropathy, as discussed earlier, but there have been no good trials of smoking cessation. However, smoking cessation should clearly be encouraged. There are no studies in diabetic kidney disease with aspirin evaluating long-term benefits, although short-term studies suggest no effect on UAE or GFR [226]. In many individuals with established CVD or high risk for CVD, aspirin should be considered for prevention of cardiovascular events. There is an increased risk of atrial fibrillation in diabetes and in CKD, and higher morbidity and mortality associated with thromboembolic events including stroke in diabetes with atrial fibrillation [227]. Where diabetes coexists with atrial fibrillation, anticoagulation is often recommended, and direct oral anticoagulants are usually preferred compared to vitamin K antagonists. In addition to a reduced risk of bleeding and similar or better effects on reducing risk of thrombosis, observational studies suggest reduction in progression of CKD. Thus, a recent study using a health claim database included persons with non-valvular atrial fibrillation and diabetes with newly initiated rivaroxaban (n = 10 017) or warfarin (n = 11 665) [228]. The participants were matched using propensity scores. In comparison to warfarin, rivaroxaban was associated with lower risks of acute kidney injury events (HR 0.83; 95% CI 0.74 to 0.92) and development of stage 5 CKD or need for haemodialysis (HR 0.82; 95% CI 0.70 to 0.96) [228]. The mechanism could be reduced vascular calcification, but that needs to be confirmed in randomized controlled trials.

Weight loss

In a trial comparing intensive lifestyle intervention with diabetes support and education in type 2 diabetes, individuals randomized to intensive lifestyle modification were less likely to develop CKD over eight years [229]. The effect was partly attributable to reductions in body weight, HbA_{1c}, and systolic blood pressure. Low-carbohydrate, Mediterranean, and low-fat diets have similar beneficial effects on change in eGFR and albuminuria over two years [230]. In individuals with type 2 diabetes who have undergone bariatric surgery, moderately and severely increased albuminuria regresses to normoalbuminuria [231]. Similar benefits were described in a five-year study in severely obese adolescents with and without type 2 diabetes [232].

Further management of chronic kidney disease stages 3–5

Monitoring anaemia and bone chemistry

In progressive CKD from stage 3 onwards, bone chemistry, full blood count, and iron stores should be assessed 3–6 monthly.

Monitoring glucose levels

Red blood cell and protein turnover are abnormal in CKD, making the interpretation of HbA_{1c}, glycated albumin, and fructosamine results difficult, particularly in people with CKD 4+. Thus, more reliance should be placed on self-monitoring of blood glucose and continuous glucose monitoring, particularly if treatment can cause hypoglycaemia [143].

Glucose-lowering agents

Metformin and its metabolites are excreted mainly by the kidney. In kidney failure, they accumulate and inhibit lactate oxidation. Metformin should therefore be used cautiously in those with eGFR <40 ml/min/1.73 m^2, and stopped completely when eGFR <30 ml/min/1.73 m^2 [233].

The sulfonylureas glibenclamide, gliclazide, and tolbutamide are excreted predominantly renally and accumulate in CKD. Their dose, and indeed the dose of any sulfonylurea, may need to be reduced as CKD progresses. Only ~10% of the meglitinides, repaglinide and nateglinide, is renally excreted, making them suitable alternative agents. The thiazolidinediones rosiglitazone and pioglitazone, are predominantly metabolized in the liver. However, their use in ESKD may be limited by fluid retention.

Insulin is also excreted by the kidney so that reduced dosage, and perhaps a switch to shorter-acting preparations, may be required.

The dose of some, but not all, dipeptidyl peptidase 4 (DPP-4) inhibitors and GLP-1RAs may need to be reduced as kidney function deteriorates. The SGLT-2 inhibitors become less effective as GFR falls. For further details see Table 44.4.

Anaemia

Anaemia is common in people with diabetes and CKD stage 3 or poorer [234]. Full investigation of iron-deficiency anaemia may be needed to exclude a non-kidney cause. Those with anaemia have higher mortality, higher rates of hospital admission with heart failure, and poorer quality of life. Iron stores should be repleted, with oral or parenteral iron as necessary, and erythropoietin replacement commenced if indicated. The Trial to Reduce cardiovascular Events with Aranesp (darbepoetin alpha) Therapy (TREAT) investigated if treatment of anaemia in people with type 2 diabetes and CKD would improve renal or cardiovascular outcome, but showed no benefit [235].

Table 44.4 Glucose-lowering agents in chronic kidney disease.

Drug	Comment
Metformin	Risk of accumulation and possibly lactic acidosis Caution when eGFR <45 ml/min/1.73 m^2 Stop when eGFR <30 ml/min/1.73 m^2
Sulfonylureas	Glibenclamide, gliclazide, and tolbutamide predominantly renally excreted; may need to reduce dose
Meglitinides	~10% excreted via kidney; usually safe
Thiazolidinediones	Predominantly hepatic metabolism; use may be limited by fluid retention
Dipeptidyl peptidase 4 inhibitors	Dose may need to be reduced in some agents
Glucagon-like peptide 1 receptor agonists	Few data when eGFR <15 ml/min/1.73 m^2
Sodium–glucose cotransporter 2 inhibitors	Protect kidney and heart down to eGFR >25, but ineffective at reducing glucose at eGFR <45 ml/min/1.73 m^2
Insulin	Excreted by kidney; may need to reduce dose and/or switch to shorter-acting preparations

eGFR, estimated glomerular filtration rate.

When to refer to nephrology

Individuals who begin dialysis as an emergency do less well than those in whom treatment is planned [236]. Referral to nephrology should be made when eGFR is declining rapidly (>5 ml/min/1.73 m^2/year or when eGFR is <30–45 ml/min/1.73 m^2). This allows structured physical and psychological preparation for kidney replacement therapy. Earlier referral may be necessary in particular circumstances (Box 44.1). The need for kidney replacement therapy should be discussed with all individuals and those who wish it should have access. People without significant comorbidities will usually be offered transplantation. Full cardiovascular assessment and treatment are essential before transplantation.

Box 44.1 Indications for referral to nephrology

Diagnosis uncertain
Hypertension difficult to control
Fluid overload
Anaemia unresponsive to oral iron
Abnormal bone chemistry
eGFR 30–45 ml/min/1.73 m^2
Nephrotic syndrome
eGFR fall >5 ml/min/1.73 m^2 per year

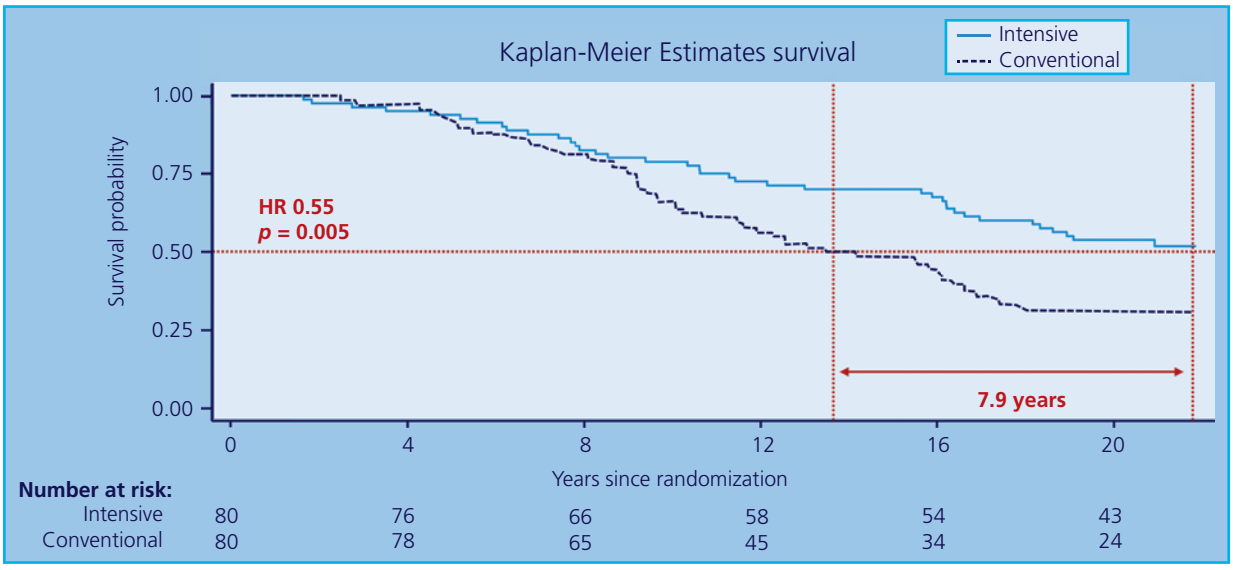

Figure 44.8 Steno-2 post-trial: 21 years' sustained effect of intensive multifactorial intervention compared to standard of care for eight years targeting lifestyle and heart and kidney risk factors. Source: Data from Gaede et al. 2016 [241].

Organization of care

Structured care, delivered by trained specialists working to clear protocols with specific, multiple treatment goals for all the variables described in this chapter, reduces the incidence of moderately elevated albuminuria [237, 238] and provides greater kidney and cardiovascular benefits than routine care for individuals with type 2 diabetes and CKD [143, 239, 240]. Progression to ESKD or death, need for laser therapy, and cardiovascular endpoints including stroke and heart failure are all reduced by such multifactorial intervention [241–244]. When structured intensive multifactorial intervention targeting lifestyle factors (diet, exercise, smoking) and heart and kidney risk factors (blood glucose, blood pressure, lipid management) compared to usual care was started in type 2 diabetes with moderately elevated albuminuria, long-term follow-up of the Steno-2 study demonstrated that eight years of intervention translated into almost eight years of extended median survival (Figure 44.8) [241].

Pregnancy in women with diabetes and chronic kidney disease

Women with diabetic nephropathy have poor pregnancy outcomes [245]. They remain at increased risk of hypertension, pre-eclampsia, abnormal fetal growth, and preterm delivery [246]. In a recent series, the prevalence of diabetic nephropathy and moderately elevated albuminuria in early pregnancy was similar in women with type 1 or type 2 diabetes, and pregnancy outcomes were comparable regardless of the type of diabetes [247]. Women with any evidence of CKD should therefore be counselled pre-pregnancy. RAS inhibitors should be stopped and therapies safe in pregnancy, such as methyldopa, labetolol, and nifedipine, substituted. In women with type 1 diabetes, maintenance of blood pressure <135/85 mmHg and proteinuria <300 mg/24 h with methyldopa improves outcomes [200, 248].

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45 Diabetic Neuropathy

Shazli Azmi[1], Uazman Alam[2], and Rayaz A. Malik[3]

[1] Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

[2]Department of Cardiovascular and Metabolic Medicine, Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, UK

[3] Department of Medicine, Weill Cornell Medicine-Qatar, Doha, Qatar

Key points

- Diabetic neuropathies are a 'heterogeneous group of disorders affecting multiple aspects of the nervous system' that can be divided into rapidly reversible neuropathies, persistent symmetrical polyneuropathies, and focal/multifocal neuropathies.
- At least one in three individuals with diabetes is affected by diabetic sensorimotor polyneuropathy, which may present with excruciating neuropathic pain and/or sensory loss leading to foot ulceration and amputation.
- Neuropathic pain markedly reduces the quality of life, by interfering with sleep and daily activities.
- Experimental studies have identified multiple pathogenetic targets for diabetic sensorimotor polyneuropathy and autonomic neuropathy, but to date no disease modifying therapies have been approved by the US Food and Drug Administration.
- Epidemiological data indicate that traditional cardiovascular risk factors such as pre-diabetes, visceral obesity, hypertension, hyperlipidaemia, and smoking play a role in the development and progression of diabetic neuropathy.
- Treatment of diabetic sensorimotor polyneuropathy is based on (i) multifactorial risk intervention targeting weight, glycaemia, blood pressure, and lipids; and (ii) symptomatic treatment of painful and autonomic symptoms.
- The management of painful diabetic sensorimotor polyneuropathy requires careful dose titration based on efficacy and side effects. Combination therapy may be useful, and potential drug interactions have to be considered given the frequent polypharmacy in people with diabetes.
- Diabetic autonomic neuropathy can cause multiple symptoms and has limited treatment options.

Classification of diabetic neuropathy

Diabetic neuropathy, as defined by the international position statement of the American Diabetes Association (ADA), is a 'heterogeneous group of disorders affecting multiple aspects of the nervous system and result[s] in a multiplicity of manifestations' [1]. Diabetic neuropathy should be actively diagnosed in people with diabetes after the exclusion of other causes of peripheral neuropathy. It may be readily apparent based on symptoms and clinical examination, or it may be demonstrated by undertaking a more detailed assessment of the somatic and/or autonomic nervous system [1]. The classification proposed by P.K. Thomas, based on anatomical and pathophysiological features, is widely used in the classification of diabetic neuropathy [2]. It distinguishes the manifestations of diabetic neuropathies into (Table 45.1):

- Rapidly reversible neuropathies.
- Persistent symmetrical polyneuropathies.
- Focal/multifocal neuropathies.

Epidemiology and clinical impact of diabetic sensorimotor polyneuropathy

The prevalence of diabetic sensorimotor polyneuropathy ranges from 20% to 90%, depending on the patient population studied and the definition of neuropathy used. Diabetic sensorimotor polyneuropathy is the most prevalent clinical manifestation in people with diabetes. In the landmark French prospective study conducted by Pirart et al. between 1947 and 1973, of 4400 adults with diabetes followed over 25 years, 50% developed diabetic sensorimotor polyneuropathy [3]. Pre-diabetes is also a risk factor for sensorimotor polyneuropathy and cardiac autonomic neuropathy [4]. In a large population-based study in the Augsburg region of Germany, the prevalence of polyneuropathy was 13.0% in participants with impaired glucose tolerance, 11.3% in those with impaired fasting glucose, and 28.0% in those with diabetes compared to 7.4% in those with normal glucose tolerance [5]. The annual incidence of diabetic sensorimotor polyneuropathy is ~2% in people with type 2 diabetes

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Table 45.1 Classification of diabetic neuropathies.

Type	Neuropathy
Rapidly reversible	Hyperglycaemic neuropathy
Persistent symmetric polyneuropathies	Distal somatic sensory/motor polyneuropathies involving predominantly large fibres
	Autonomic neuropathies
	Small-fibre neuropathies
Focal/multifocal neuropathies	Cranial neuropathies/
	Thoracoabdominal radiculopathies/
	Focal limb neuropathies/
	Proximal neuropathies
	Compression and entrapment neuropathies

(UK Prospective Diabetes Study, UKPDS) and people with type 1 diabetes (Diabetes Control and Complications Trial, DCCT) [6].

Based on natural history studies, risk factors for the progression of diabetic sensorimotor polyneuropathy in type 1 diabetes and type 2 diabetes include suboptimal glycaemic management, age, duration of diabetes, visceral obesity or body mass index (BMI), height, hypertension, smoking status, hypoinsulinaemia, and dyslipidaemia, particularly hypertriglyceridaemia [6–10]. The major clinical manifestations of diabetic sensorimotor polyneuropathy include neuropathic pain, sensory loss, and impaired gait [11], which are associated with depressive symptoms [12]. Vibration perception threshold and nerve conduction velocity predict mortality [13, 14] and foot ulceration [15]. Foot ulceration is a common cause of hospital admission in people with diabetes and 80% of lower-limb amputations occur as a direct consequence of non-healing foot ulcers (Chapter 53).

In the Early Treatment Diabetic Retinopathy Study (ETDRS), mortality in individuals with type 2 diabetes was related to the presence of macrovascular disease, worsening microvascular disease, and diabetic sensorimotor polyneuropathy [16]. In a community-based study from the UK, diabetic sensorimotor polyneuropathy defined by reduced touch or pressure sensation was associated with incident non-fatal myocardial infarction, need for coronary revascularization, congestive cardiac failure, transient ischaemic attack and stroke, and, indeed, the addition of diabetic sensorimotor polyneuropathy in a model based on standard cardiovascular disease risk factors improved cardiovascular risk prediction [17]. The presence of neuropathy in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was the strongest predictor of mortality in people with type 2 diabetes allocated to intensive glycaemic management with a glycated haemoglobin (HbA_{1c}) <6.0% (42 mmol/mol) [18]. Myocardial ischaemia detected using sestamibi single-photon emission computed tomographic imaging was strongly associated with diabetic sensorimotor polyneuropathy [19]. In a prospective cohort study of people without diabetes from the USA, neuropathy was independently associated with mortality [20].

Diabetic sensorimotor polyneuropathy remains underdiagnosed by physicians and underreported by people with diabetes. In a study from Japan, physicians were only aware of painful diabetic neuropathy in ~36.4% of the individuals with the condition [21]. In a population-based survey (KORA F4) from Germany, 77% of people with diabetic sensorimotor polyneuropathy were unaware of the diagnosis and a quarter had not had a foot examination [22]. In the PROTECT study, painful and painless diabetic sensorimotor polyneuropathy were undiagnosed in 57% and 82% of people with type 2 diabetes, respectively [23], and in a follow-up study 33% of people with painful diabetic neuropathy had not received treatment [24]. In two studies from Qatar, despite a high prevalence of diabetic sensorimotor polyneuropathy (23%) [25] and painful diabetic sensorimotor polyneuropathy (34.5%) [26], 80% of the individuals had not been previously diagnosed [27].

Neuropathic pain is often the primary complaint that motivates people to seek medical advice. It has a significant impact on sleep and interferes with daytime social functioning and work [11]. Despite severe symptoms it is frequently unreported and inadequately treated [28]. A UK-based study demonstrated that 13% had never reported their symptoms of painful diabetic neuropathy to their treating physician and ~40% had never received treatment [28]. In a large population-based study in the North West of England, one-third of all community-based people with diabetes had painful neuropathic symptoms [29]. In another community-based study in Augsburg, Germany (MONICA/KORA Augsburg Surveys S2 and S3), the prevalence of painful neuropathy was 13.3% in people with diabetes, 8.7% in impaired glucose tolerance, and 4.2% in impaired fasting glycaemia compared to 1.2% in those with normal glucose tolerance [30]. People with ischaemic heart disease also have excess neuropathic pain [31]. Risk factors for neuropathic pain include age, obesity, and low physical activity [26]. Pain treatments include antidepressants (~44%), anticonvulsants (~17%), opiates (~39%), or other drugs (~30%) [28]. Opiates are of considerable concern, given their limited efficacy for painful diabetic neuropathy and risk of long-term dependency and misuse [21, 32]. A 30–50% reduction in pain is considered adequate, whereas a ≥50% improvement in pain is considered a good outcome [33]. Neuropathic pain tends to persist to some degree in the majority of individuals with diabetes.

Clinical manifestations of diabetic neuropathy

Diabetic sensorimotor polyneuropathy

Diabetic sensorimotor polyneuropathy is defined as a 'symmetrical, length-dependent sensorimotor polyneuropathy which occurs as a consequence of metabolic and microvascular alterations due to chronic hyperglycaemia of diabetes (or prediabetes) and cardiovascular risk factors' [34]. The onset of diabetic sensorimotor polyneuropathy is usually insidious and without early intervention there is progression to more advanced stages with a poor prognosis. It is length dependent, with the terminal portions of the axons being more vulnerable with initial involvement of the toes and feet followed by the fingers and hands (*glove and stocking distribution*), and it is associated with height (Figure 45.1) [35]. In more advanced diabetic sensorimotor polyneuropathy, the anterior abdominal wall and lateral trunk may also be affected. Peripheral nerves comprise large-fibre myelinated (Aα, Aβ fibres), thinly myelinated (Aδ fibres), and small-fibre unmyelinated (C fibres) nerves. At present, the general consensus is that small fibres are involved first, followed by large-fibre dysfunction. Studies in both type 1 diabetes and type 2 diabetes have demonstrated pathological reductions in small nerve fibres with normal nerve conduction studies [36, 37]. The early involvement of small nerve fibres is based on individuals presenting with pain and hyperalgesia (Aδ and C fibres) and reduction in corneal and intraepidermal nerve fibres prior to abnormalities of nerve conduction in adults with type 1 diabetes and type 2 diabetes [38], those with impaired glucose tolerance [39], and children with type 1 diabetes [40].

Sensory ataxia (ataxic gait) may occur in diabetic sensorimotor polyneuropathy with a loss or reduction in touch, pressure, and vibration sensation, although this represents a more severe end of the spec-

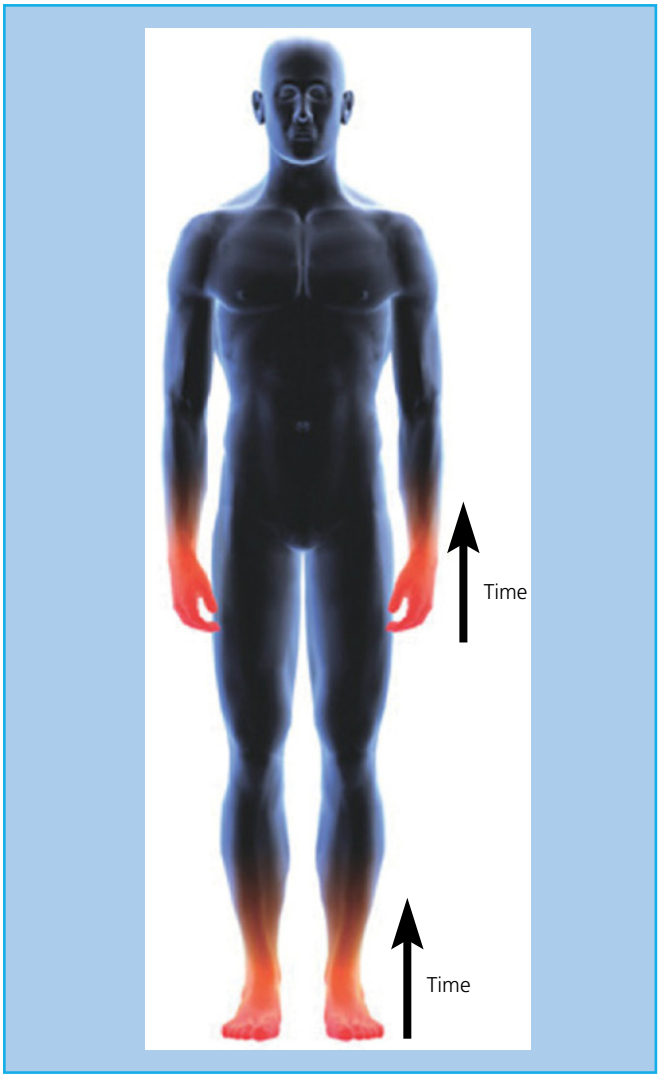

Figure 45.1 The typical 'glove-and-stocking' distribution of diabetic distal symmetrical sensory or sensorimotor polyneuropathy.

Figure 45.2 A typical example of the distribution of sensory deficits in a person with distal symmetrical sensorimotor polyneuropathy. Dots, reduced thermal sensation; lines, reduced pain sensation; crossed lines, reduced touch sensation.

trum. The distribution of sensory deficits classically seen in diabetic sensorimotor polyneuropathy is shown in Figure 45.2. Symptoms are often defined as *positive* sensory symptoms (paraesthesia, dysaesthesia, and characteristic neuropathic pain) or *negative* symptoms (reduced sensation); however, these symptoms may coexist. There are several variants of diabetic sensorimotor polyneuropathy, including acutely painful small-fibre or pseudosyringomyelic syndromes and an ataxic syndrome (tabes dorsalis).

Neuropathic pain may be continuous or episodic and characteristically worsens at night, resulting in disturbed sleep [41]. Neuropathic pain may also improve during exercise or walking, which can help to differentiate it from ischaemic pain [42]. Nocturnal exacerbation with increased pain intensity, especially when tired or stressed, is also a typical phenotypic feature of painful neuropathy [43]. Pain from diabetic sensorimotor polyneuropathy may continue over many years [28, 44], resulting in considerable morbidity [11], but it may improve partially or entirely in some, despite worsening nerve function [45]. The prevalence of pain is higher in individuals with worse neuropathy [29], with recent studies showing greater small-fibre damage in those with painful compared to painless diabetic neuropathy [46, 47]. Pain remission is associated with a shorter duration of pain or diabetes and lesser severity of diabetic sensorimotor polyneuropathy [45].

It is important to exclude other pathologies that may present with symptoms similar to diabetic sensorimotor polyneuropathy by taking a detailed history and careful examination [48]:

- The pain of *intermittent claudication* is typically exacerbated by walking, while it is relieved in diabetic polyneuropathy, and can occur in the thighs and buttocks, unless it is diabetic lumbosacral plexopathy.
- The pain of *Charcot neuroarthropathy* occurs with collapse and deformity of the foot bones, with increasing warmth in the foot due to inflammation in the presence of a severe neuropathy.
- The pain of *plantar fasciitis* occurs with each heel step and is associated with exquisite tenderness in the sole of the foot.
- The pain of *osteoarthritis* occurs in the feet and hands, is associated with morning stiffness, exacerbated with joint movement and/or exercise, and improves with ambulation during the day.

Overt motor neuropathy is less frequent and most often restricted to the distal lower limbs. Ankle reflexes are frequently reduced or absent with motor involvement. Muscle atrophy and weakness occur in tandem and are largely present at the toes and feet [49], leading to abnormal loading (foot pressures) that is a risk factor for

ulceration [50]. However, significant reductions in strength with lower-limb muscle atrophy have been demonstrated in individuals with impaired glucose tolerance [51] and mild diabetic neuropathy [52], leading to altered gait and walking strategy [53].

The loss of the protective sensation (insensate feet), muscle atrophy, and autonomic involvement with reduced sweat production results in dry skin with callus, which increases the risk of ulceration. Foot complications can be severe and potentially life-threatening as a consequence of ulceration, Charcot neuroarthropathy, and osteomyelitis, with non-healing ulcers leading to lower-limb amputation [54]. Lower-limb amputation rates are 15 times higher in people with diabetes compared to those without diabetes [54]. The active detection of diabetic sensorimotor polyneuropathy is imperative, given that a large proportion of individuals are asymptomatic or remain undiagnosed [26]. Unfortunately, current guidelines [1] advocate the use of simple tests such as the monofilament, which can only detect advanced diabetic sensorimotor polyneuropathy and those at high risk of foot ulceration [55].

Acute painful neuropathy

Acute painful neuropathy occurs in both type 1 diabetes and type 2 diabetes and has been described as a separate clinical entity to diabetic sensorimotor polyneuropathy [56]. The characteristic presentation is of continuous burning pain, particularly on the plantar aspect of the feet, with nocturnal exacerbation. It is often described as being 'like walking on burning sand'. A typical phenotypic picture includes predominantly positive symptoms such as hypersensitivity to tactile stimuli (allodynia), such as pain on contact with bed sheets, and hyperalgesia. Erectile dysfunction and depression are common comorbid conditions. Motor function tends to be preserved with a paucity of sensory loss. Severe weight loss may precede its onset and was originally coined *diabetic cachexia* by Ellenberg [57]. Weight loss improves with better glycaemic management, and severe manifestations subside within 10–12 months, with no recurrence observed on follow-up over six years [56].

In 1933 Caravati [58] coined the term *insulin neuritis* after he described a case of acute painful neuropathy following the initiation of insulin treatment and rapid improvement in glycaemic levels. The terminology of this disorder has now changed to treatment-induced neuropathy in diabetes, whereby a sudden improvement in glycaemic levels in people with marked hyperglycaemia manifests as small-fibre neuropathy with neuropathic pain and varying degrees of autonomic neuropathy [59]. Gibbons et al. [60] showed that the absolute risk of treatment-induced neuropathy in diabetes increased with the degree of decline in HbA_{1c}:

- Reduction in HbA_{1c} of 2–3% (22–33 mmol/mol) over three months = 20% absolute risk.
- Reduction in HbA_{1c} of >4% (44 mmol/mol) over three months >80% absolute risk.
- Reduction in HbA_{1c} of >5% (55 mmol/mol) over three months >90% absolute risk.

The extent of HbA_{1c} reduction was also related to the distribution and severity of pain and autonomic dysfunction, retinopathy, and microalbuminuria [60]. Histopathological studies have demonstrated severe nerve fibre loss with unmyelinated fibre degeneration and regeneration in sural nerve biopsies [61] and epineurial arteriovenous shunting with neovascularization similar to proliferative diabetic retinopathy, which we proposed may have occurred as a consequence of endoneurial ischaemia [59]. Reassuringly, the painful symptoms tend to improve over 3–8 months while maintaining optimal glycaemic levels.

Focal and multifocal neuropathies

Focal and multifocal neuropathies occur in older people with a longer duration of diabetes. They tend to be self-limiting, with either partial or complete recovery and resolution of pain [62]. These individuals should be reassured that recovery will occur with conservative treatment.

Cranial neuropathy

A large registry study from the Middle East and North Africa region showed that the prevalence of ophthalmoplegia secondary to diabetes was ~0.32% [63]. Third nerve palsy was the most common (~53%) and was painful in about 50% of cases [63]. It is characterized by sudden-onset retro-orbital and supra-orbital pain, which may precede ptosis and diplopia (with pupillary dysfunction in 14–18% of cases). Ophthalmoplegia can persist for a number of weeks, with full recovery occurring usually within 12 weeks [64]. The 4th, 6th, and 7th cranial nerves can also be affected. The most important risk factors are age over 45 years, diabetes duration greater than 10 years, male sex, and presence of retinopathy and nephropathy [63].

Mononeuropathy of the limbs

The ulnar, median, radial, and peroneal nerves and to a lesser extent truncal nerves are affected and can be acutely painful. Entrapment neuropathies, such as carpal tunnel syndrome, are also more common in people with diabetes. Carpal tunnel syndrome is associated with painful paraesthesia in the hand, but can extend to the shoulder [65].

Diabetic truncal neuropathy

Diabetic thoracoabdominal neuropathy or radiculopathy presents primarily in middle-aged or older individuals and is characterized by sudden onset of pain or dysaesthesia, occasionally accompanied by hyperaesthesia. Pain may be described as burning, tearing, jabbing, and boring and is usually worse at night. Diabetic truncal neuropathy is almost always unilateral, half encircling the trunk in a root-like distribution. Peak pain occurs a few days after onset, but may continue for weeks to months. Depending on the site of the pain, it may be confused with a pulmonary, cardiac, or gastrointestinal origin for the pain. Abdominal muscle herniation is a rare feature and occurs predominantly in middle-aged men, involving 3–5 adjacent nerve roots between T6 and T12 (Figure 45.3a). Weight loss is a recognized phenomenon, with 7–18 kg loss occurring in >50% of cases [66]. This should alert the physician to exclude underlying malignancy. The prognosis of truncal neuropathy is good, with remission usually within 16 weeks [67].

Diabetic amyotrophy

Diabetic amyotrophy, also known as proximal motor neuropathy, proximal diabetic neuropathy, diabetic lumbosacral plexopathy, or femoral neuropathy, commonly presents with unilateral proximal muscle weakness and wasting of the obturator, iliopsoas, adductor, and quadriceps muscles (Figure 45.3b). The pain is constant, severe, deep, aching, and burning, with nocturnal exacerbation, and is often refractory to standard analgesia including high-dose opiates. Characteristically, it occurs in the lower back or buttock on the affected side, or may be felt as extending from the hip to the knee [68]. There is frequently associated cachexia with substantial weight loss, which tends to be regained during the recovery phase [69].

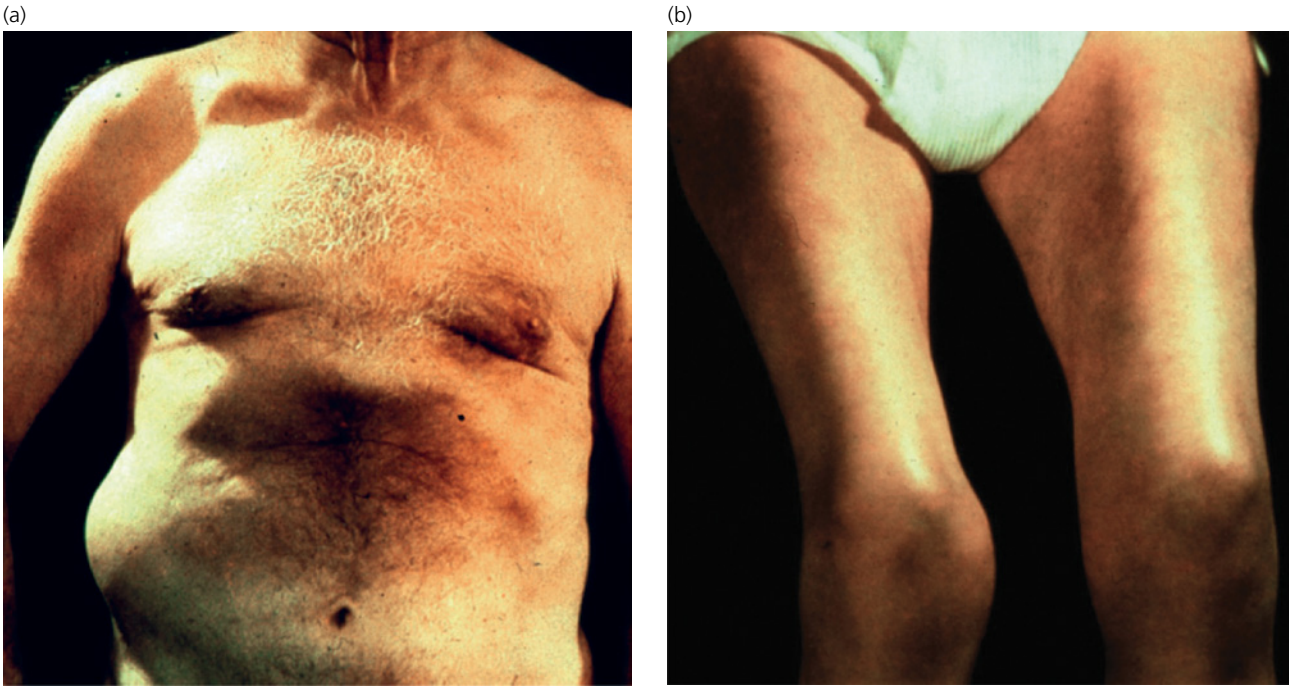

Figure 45.3 (a) Diabetic truncal neuropathy (thoracoabdominal neuropathy or radiculopathy) leading to herniation of the oblique abdominal muscle. (b) Diabetic amyotrophy (proximal neuropathy): pronounced bilateral atrophy and paresis of the quadriceps muscle.

Central nervous system abnormalities in structure and function

Early post-mortem studies demonstrated extensive neurodegeneration in the cerebral cortex, midbrain, and cerebellum [70, 71]. *In vivo* brain imaging has confirmed widespread structural and functional alterations in the brain of individuals with diabetic sensorimotor polyneuropathy without overt cerebrovascular disease [72–76]. Anatomical and functional changes within the somatosensory cortex [73] and spinal cord [77] and a reduction in spinal cord cross-sectional area at C4/5 and T3/4 have been demonstrated in individuals with diabetic sensorimotor polyneuropathy [78]. Magnetic resonance imaging has also shown an excess of subcortical and brainstem lesions in people with type 1 diabetes and diabetic sensorimotor polyneuropathy [79]. In a functional magnetic resonance imaging (fMRI) study, peripheral thermal stimulation was associated with increased activation in somatosensory (right insula, left caudate nucleus, frontal gyrus, and cingulate cortex) and cognition-related (right temporal lobe, left hippocampus, and left fusiform gyrus) cerebral areas of people with diabetic sensorimotor polyneuropathy [80]. Individuals with painful diabetic neuropathy demonstrate enhanced limbic and striatal activation, suggesting a central nervous system contribution to the development and maintenance of neuropathic pain [81]. A study utilizing fMRI and quantitative sensory testing showed altered functional connectivity in the ventrolateral periaqueductal grey of individuals with painful diabetic neuropathy [82].

The Maastricht study showed that people with pre-diabetes had increased lacunar infarcts and white matter hyperintensities independent of major cardiovascular risk factors, which was comparable to 2.1 years of brain ageing [83]. A larger population-based study confirmed that pre-diabetes was associated with smaller total and white matter volume and pre-diabetes and diabetes were both independently associated with accelerated cognitive decline [84]. Weinstein et al. [85] showed reduced occipital grey matter volume and white matter integrity in adults with pre-diabetes. We have recently also shown that corneal nerve loss is associated with the presence of white matter hyperintensities [86] and cognitive decline in individuals with mild cognitive impairment and dementia [87, 88].

Several studies have assessed central nervous system function utilizing event-related potentials, evoked potentials in response to stimulation of peripheral nerves and neuropsychological assessment. Zeigler et al. [89] showed somatosensory afferent pathway dysfunction in people with type 1 diabetes, which was related to the severity of diabetic neuropathy and characterized by neuroplasticity and alteration of the cortical sensory complex and peripheral rather than spinal or supraspinal deficits [89]. Zeigler et al. [90] have also utilized positron emission tomography (PET) and [^{18}F]-2-deoxy-2-fluoro-D-glucose (FDG) to show a reduction in cerebral glucose metabolism in individuals with type 1 diabetes and diabetic sensorimotor polyneuropathy compared to individuals with newly diagnosed type 1 diabetes and healthy volunteers. The thalamus modulates information from the periphery to the somatosensory cortex, with ascending sensory pathways in the spinal cord terminating within the ventroposterior lateral thalamic subnucleus before high-order sensory projections are sent to the cortex [91]. Proton magnetic resonance spectroscopy studies have demonstrated abnormalities in brain metabolites with a lower *N*-acetyl aspartate-to-creatine ratio, suggesting thalamic neuronal dysfunction in diabetic sensorimotor polyneuropathy [92].

Pathogenesis of diabetic sensorimotor polyneuropathy

The pathogenesis of diabetic neuropathy is multifactorial [1, 93, 94], with interactions between metabolic and vascular factors:

- Increased flux through the polyol pathway, leading to accumulation of sorbitol and fructose, *myo*-inositol depletion, and reduction in Na^+K^+-ATPase activity.

- Disturbances in n-6 essential fatty acid and prostaglandin metabolism, altering nerve membrane structure and lead to microvascular and blood flow abnormalities.
- Endoneurial microvascular disease with hypoxia, generation of reactive oxygen species (oxidative stress), activation of the redox-sensitive transcription factor NFκB, and increased activity of protein kinase C (PKC).
- Reduced expression of neurotrophic factors such as nerve growth factor (NGF), neurotrophin-3 (NT-3), and insulin-like growth factor (IGF) and alterations in axonal transport.
- Accumulation of non-enzymatic advanced glycation end-products (AGEs) on nerve and/or vessel proteins.
- Immunological processes with autoantibodies to the vagal nerve, sympathetic ganglia, and adrenal medulla.
- Cytokine activation with increased interleukin 2 (IL-2), IL-6, tumour necrosis factor α (TNF-α), and inflammation.

Diagnosis of diabetic sensorimotor polyneuropathy

The assessment of diabetic neuropathy must include a careful and focused history. The symptomology of diabetic sensorimotor polyneuropathy depends on the type of nerve fibre involved, with large-fibre dysfunction leading to numbness, tingling, or poor balance, whereas small-fibre neuropathy leads to paraesthesia and burning, stabbing, or electric shock–like pain in the feet [28, 30]. Alternative aetiologies of neuropathy should be actively diagnosed and treated, including chronic inflammatory demyelinating polyneuropathy (CIDP), vitamin B_{12} deficiency, hypothyroidism, and uraemia [95]. Screening for neuropathy should begin from diagnosis in people with type 2 diabetes, and after five years in those with type 1 diabetes and in people with pre-diabetes and neuropathic symptoms [1].

There are several tests for the assessment of diabetic sensorimotor polyneuropathy (Table 45.2). The Neuropathy Disability Score (NDS) is a reliable and reproducible screening tool to identify the presence and severity of neuropathy (Figure 45.4). It involves testing sensory modalities including pain sensation (pin-prick), temperature perception (using hot and cold rods), vibration (128 Hz tuning fork), and tendon reflexes, with an NDS of >6/10 being an independent risk factor for foot ulceration [96]. All individuals should undergo an annual 10 g monofilament and pedal pulse evaluation to assess for the risk of foot ulceration [1]. However, a normal response to the 10 g monofilament should not be used to exclude diabetic sensorimotor polyneuropathy, as it only detects advanced neuropathy. In a recent systematic review it had a very poor diagnostic utility, with a sensitivity of 88% and specificity of only 55%, when nerve conduction was used to diagnose diabetic neuropathy [97]. The alternative 1 g monofilament may be better for detecting earlier neuropathy [98].

Diagnostic definitions

In 2010 the Toronto Diabetic Neuropathy Expert group [34] defined diabetic sensorimotor polyneuropathy as:

- *Confirmed* – abnormal nerve conduction and a symptom or sign of neuropathy.
- *Probable* – two or more of the following: neuropathic symptoms, decreased distal sensation, or decreased/absent ankle reflexes.
- *Possible* – any of the following symptoms: decreased sensation, positive neuropathic sensory symptoms (e.g. numbness while sleeping, prickling/stabbing, burning or aching pain) predominantly in the toes, feet, or legs, OR signs of symmetrical decrease of distal sensation or decreased/absent ankle reflexes.

Small-fibre abnormality can be diagnosed using the following criteria [34]:

- *Definite* – presence of length-dependent symptoms, clinical signs of small-fibre damage, normal sural nerve conduction, and reduced intra-epidermal nerve fibre density at the ankle and/or abnormal thermal thresholds at the foot.
- *Probable* – presence of length-dependent symptoms, clinical signs of small-fibre damage, and normal sural nerve conduction.
- *Possible* – presence of length-dependent symptoms and/or clinical signs of small-fibre damage.

Table 45.2 Tests to assess diabetic peripheral neuropathy.

	Advantage	Disadvantage	Type of nerve
Nerve conduction studies	Sensitive, specific, reproducible, and easily standardized	Must be done by trained professional Only assesses large-fibre damage	Large fibre
Quantitative sensory testing	Reproducible and reliable	Subjective	Large and small fibre
Skin biopsy	Gold standard, reliable, and reproducible	Invasive procedure Needs specialized laboratory service	Small fibre
Corneal confocal microscopy	Rapid, reproducible, non-invasive Can detect small-fibre damage and track progression	Must be done by trained professional	Small fibre
Sudoscan	Non-invasive, easy to perform, and very quick (<5 min) No specialist training of assessor required	Low specificity	Small fibre
Laser Doppler imaging FLARE	Non-invasive Sensitive, specific	20 min to perform the procedure due to heating of the skin	Small fibre

Neuropathy symptoms

Questionnaires are a subjective method to assess and quantify the severity of neuropathic symptoms and pain. The McGill Pain Questionnaire is widely used to evaluate neuropathic pain [99]. There are also other questionnaires specifically developed to quantify neuropathic pain, which include the Brief Pain Inventory (BPI) [100], Neuropathic Pain Questionnaire (NPQ) [101], Neuropathic Pain Symptom Inventory (NPSI), and Douleur Neuropathique 4 (DN4) [102]. The Neuropathic Symptom Profile (NSP) has been validated to stage the severity of neuropathy [103].

Quantitative sensory testing

Quantitative sensory testing is a psychophysical method used to quantify somatosensory function in response to controlled stimuli [104]. It is a sensitive method of detecting small-fibre neuropathy, particularly in those individuals with normal nerve conduction studies [105], and may be used where no definitive quantitative structural

Figure 45.4 Measurement of temperature sensation using cold and warm rods (a), Achilles tendon reflex (b), pain sensation using a Neurotip (c), and vibration perception using a tuning fork (d).

assessment of small nerve fibres such as skin biopsy or corneal confocal microscopy (CCM) can be undertaken, as well as for monitoring of somatosensory deficits, and of evoked pain, allodynia, and hyperalgesia. When performing quantitative sensory testing, it has been recommended to use predefined standardized stimuli and instructions, validated algorithms for testing, and reference values corrected for anatomical site, age, and sex. The interpretation should always take into account the clinical context, individuals with language and cognitive difficulties, and anxiety [68, 104].

Vibration perception threshold

Vibration perception threshold can be assessed using a hand-held biothesiometer and correlates with the severity of diabetic neuropathy. A vibration perception threshold of >25 V is a strong predictor for incident foot ulceration [106].

Nerve conduction studies

Nerve conduction studies (Figure 45.5) are an objective, sensitive, specific, and reproducible method to assess the severity of diabetic sensorimotor polyneuropathy [107]. However, they only evaluate large myelinated nerve fibres and cannot detect early small-fibre neuropathy and have relatively high intra-individual variability based on electrode placement and limb temperature [108].

Skin biopsy

Skin biopsy can be used to quantify intra-epidermal and dermal nerve fibres and autonomic nerve fibres. It enables direct visualization of thinly myelinated and unmyelinated nerve fibres, which are

Figure 45.5 Nerve conduction studies.

the earliest to be affected in diabetic polyneuropathy (Figure 45.6). The European Federation for Neurological Societies recommends a punch skin biopsy at the distal leg or proximal thigh for the diagnosis of small-fibre neuropathy [109]. For diagnostic purposes in peripheral neuropathies, the guideline recommends performing a 3 mm punch skin biopsy at the distal leg and quantifying the linear density of intra-epidermal nerve fibres (IENF) in at least three 50 µm thick sections per biopsy, by bright-field immunohistochemistry or immunofluorescence with anti-protein gene product 9.5 antibodies (PGP 9.5) (Figure 45.7). The assessment of IENF and their densities (IENFD) is currently advocated in the assessment of idiopathic small-fibre neuropathy (ISFN) [110].

Corneal confocal microscopy

Corneal confocal microsopy (CCM) (Figure 45.8) is a rapid, non-invasive, objective, and reproducible ophthalmic imaging technique used to evaluate corneal nerve morphology and has been established as a surrogate marker for peripheral neuropathies [111]. CCM allows direct visualization of peripheral nerves [112, 113], with high sensitivity and specificity to diagnose [38, 114, 115] and predict the development [116] and progression [117] of diabetic sensorimotor polyneuropathy (Figure 45.9) and repair after intervention [118–120]. CCM correlates with IENFD [114] and has comparable sensitivity and specificity to IENFD for the diagnosis of diabetic sensorimotor polyneuropathy [37, 121]. The parameters used to quantify the corneal sub-basal nerve plexus include corneal nerve fibre length (CNFL), corneal nerve branch density (CNBD), and corneal nerve fibre density (CNFD) [122]. CCM has been extensively used to identify small nerve fibre damage in a range of peripheral neuropathies including diabetic neuropathy [123, 124], HIV neuropathy [125], chemotherapy-induced peripheral neuropathy (CIPN) [126], CIDP [127], Fabry's disease [128], and ISFN [129]. CCM can detect subclinical small nerve fibre damage in those with impaired glucose tolerance [130] and children with type 1 diabe-

Figure 45.6 Skin punch biopsy and immunohistochemistry testing.

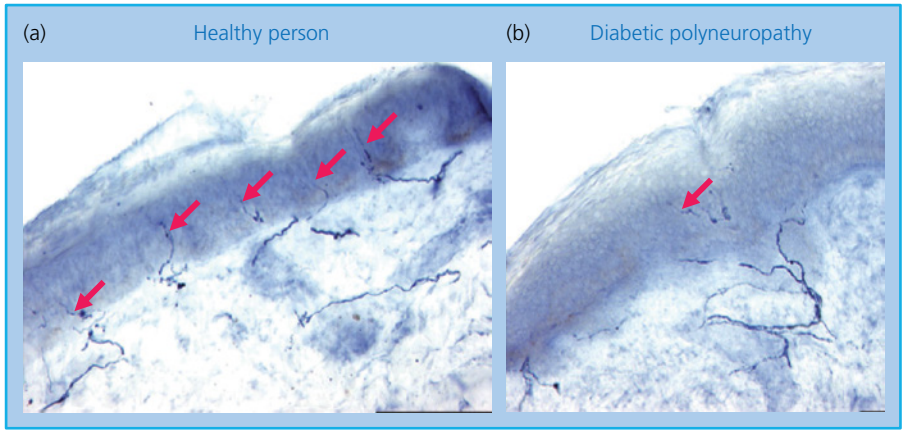

Figure 45.7 (a) Loss of intraepidermal nerve fibres in skin biopsy from the lateral lower leg in a person with diabetes with polyneuropathy compared with (b) a healthy person without diabetes (red arrows indicate intraepidermal nerve fibre). Bright-field immunohistochemistry with anti-protein gene product 9.5 antibodies (PGP 9.5).

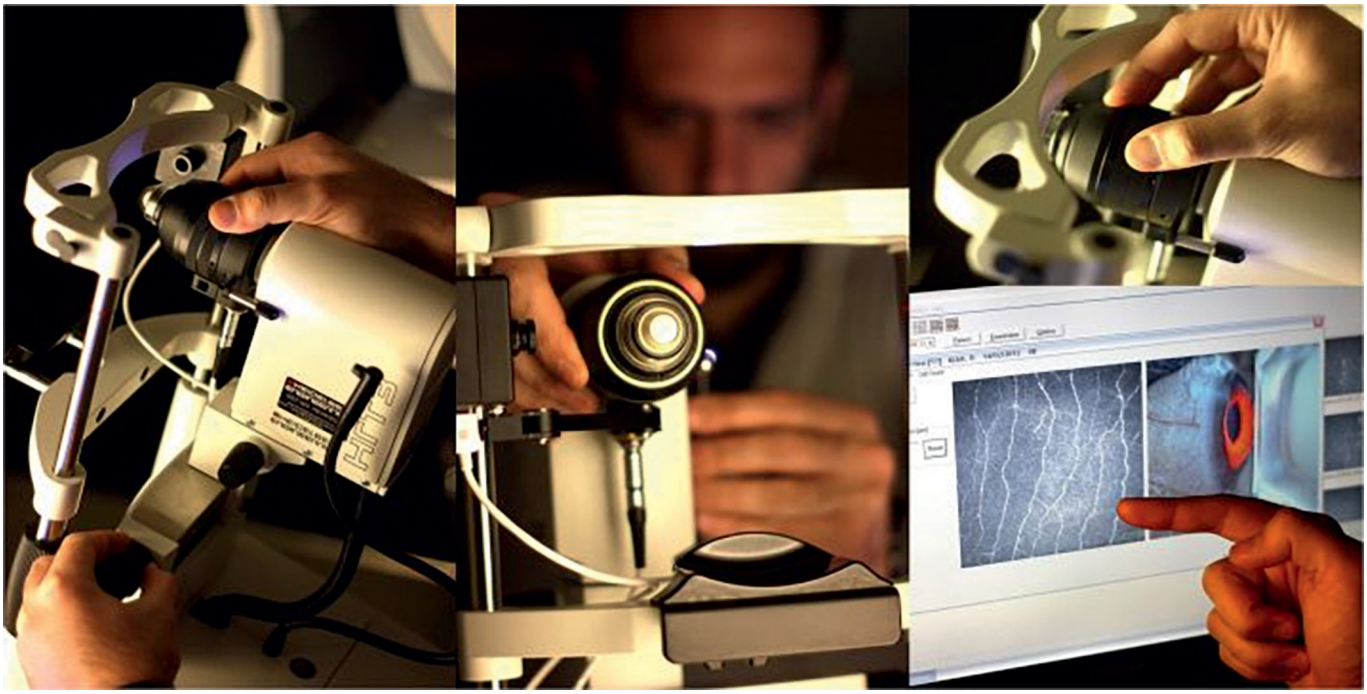

Figure 45.8 Corneal confocal microscopy.

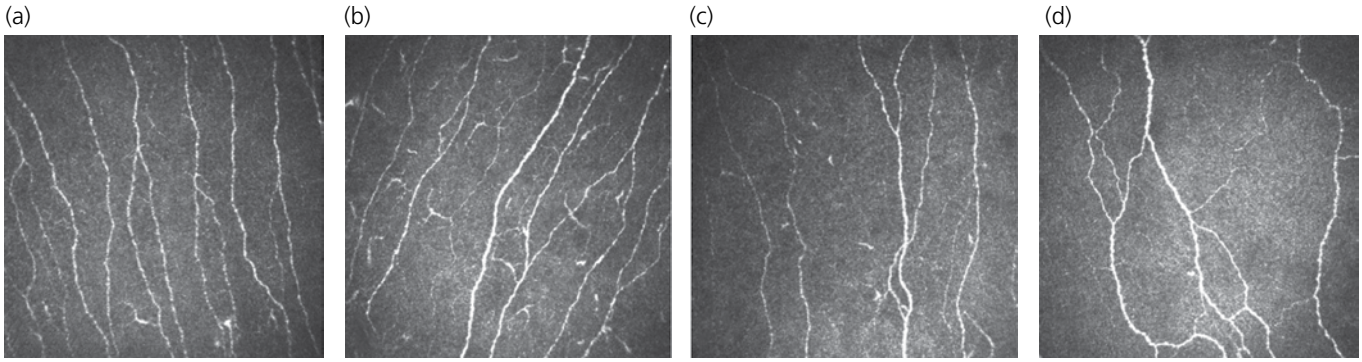

Figure 45.9 Images of corneal nerves from a person with no (a), mild (b), moderate (c), and severe (d) neuropathy.

tes [40]. A reduction in corneal nerve fibres is also associated with the development of neuropathy [131] and foot ulceration with Charcot foot [132]. CCM may be an ideal technique to monitor progression of diabetic neuropathy as it is non-invasive and hence reiterative [133].

Optical coherence tomography

Optical coherence tomography is an imaging technique commonly available in most ophthalmology clinics and was developed for *in vivo* assessment of the retina to assess macular oedema. It has been used to quantify retinal nerve fibre layer loss in individuals with multiple sclerosis [134, 135]. Retinal nerve fibre layer loss has been reported in increasing severity of diabetic neuropathy [136] and was greater in individuals with compared to without diabetic neuropathy over four years [137]. Longitudinal and prognostic as well as interventional studies using optical coherence tomography as a surrogate marker of axonal loss are required before routine use of this modality can be recommended to assess diabetic neuropathy.

Sudoscan

Sudoscan uses galvanic principles [138, 139] by applying a low-voltage current to measure sweat gland function based on sweat chloride concentrations using reverse iontophoresis and chronoamperometry [140] to measure the electrochemical skin conductance on the hands and feet. It is non-invasive and easy to perform within five minutes in a clinical setting [138] and has been suggested as a potential screening tool for diabetic sensorimotor polyneuropathy and cardiac autonomic neuropathy during annual assessment in a diabetes clinic [138, 141].

Laser doppler imaging FLARE

Laser Doppler imaging FLARE (LDI FLARE) measures axon-mediated neurogenic vasodilatation using laser Doppler imaging in response to heating the skin on the dorsum of the foot to 44 °C [142]. It is sensitive and specific for early small-fibre neuropathy in diabetes [142, 143]. The main disadvantage of LDI FLARE is that it takes 20 minutes to undertake the procedure [142].

Management

Intensive diabetes therapy and metabolic factors

Several landmark studies have shown that intensive glycaemic management can prevent or delay the progression of neuropathy in people with type 1 diabetes [144]. HbA_{1c}, smoking status, and high-density lipoprotein cholesterol are associated with neuropathy [145, 146]. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (ESDR) reported a 20% decrease in the incidence of diabetic sensorimotor polyneuropathy for a 2% (22 mmol/mol) decrease in HbA_{1c} over 4 years of follow-up [147]. The DCCT showed a 64% risk reduction for incident diabetic sensorimotor polyneuropathy with intensive glucose management over 6.5 years of follow-up [148]. The EDIC study confirmed the role of metabolic memory as, despite HbA_{1c} in the two groups being similar (8.1% vs 8.2%; 65% vs 67 mmol/mol) at 5 years after close-out of the DCCT, the prevalence and incidence of diabetic sensorimotor polyneuropathy and cardiac autonomic neuropathy remained significantly lower in individuals on intensive compared to standard therapy [149].

However, in people with type 2 diabetes, the situation is more complex and the evidence for the role of improved glycaemic management in slowing down progression of neuropathy is limited [150–152]. Although the ACCORD trial showed a significant reduction in loss of sensation to light touch after five years of intensive glycaemic management (HbA_{1c} <6.5%; 48 mmol/mol), this was only one of four neuropathy endpoints that improved [151]. Furthermore, the intensive glucose-lowering regimen was associated with increased overall mortality (hazard ratio 1.22, 95% confidence interval [CI] 1.01 to 1.46, p = 0.04) [153]. Self-reported diabetic sensorimotor polyneuropathy conferred a higher risk of mortality in the intensive glycaemic management group than higher HbA_{1c} and those on aspirin [18].

There is an association between plasma triglycerides and remnant lipoproteins and the risk of diabetic sensorimotor polyneuropathy [8]. Statins, ezetimibe, and fibrates may reduce the progression and severity of diabetic neuropathy [154, 155].

Diet and behavioural interventions

The Diabetes Prevention Program demonstrated that behavioural changes and treatment with metformin reduced the incidence of diabetes in those with impaired glucose tolerance [156]. In the Impaired Glucose Tolerance Causes Neuropathy study, diet and exercise counselling according to the Diabetes Prevention Program protocol in those with impaired glucose tolerance resulted in increased IENFD and an improvement in neuropathic pain [157].

Weight loss

Incretin-based therapies have valuable effects on diabetes-related complications, independent of their glucose-lowering abilities, mainly mediated by their anti-inflammatory and anti-oxidative stress properties [158]. In a pilot study of people with type 2 diabetes and mild to moderate diabetic sensorimotor polyneuropathy, 18 months of treatment with exenatide, compared with glargine, had no effect on the Michigan Neuropathy Screening Instrument and IENFD [159]. However, a recent randomized controlled trial (RCT) has shown that once-weekly exenatide and pioglitazone or basal bolus insulin resulted in a ~3% (33 mmol/mol) reduction in HbA_{1c} and corneal nerve regeneration, despite a ~4 kg weight gain [160].

In a meta-analysis of 10 studies, there was greater remission and lower risk of microvascular and macrovascular disease and mortality over five years in individuals undergoing bariatric surgery [161]. Bariatric surgery is associated with corneal nerve regeneration within 12 months in those with morbid obesity, both with [120] and without diabetes [162].

Disease-modifying treatment

Pancreas transplantation for type 1 diabetes improves nephropathy and retinopathy [163, 164]. A 10-year follow-up of neuropathy post-transplantation showed an improvement in sudomotor function in the hand and foot within one year, which was maintained throughout 10 years. However, there was no impact on nerve conduction velocity or autonomic function [165, 166]. We initially showed regeneration of corneal nerves within six months of simultaneous pancreas and kidney transplantation in individuals with type 1 diabetes and severe diabetic sensorimotor polyneuropathy [118, 167]. Recently we have shown that the early improvement in small nerve fibres is followed by an improvement in symptoms at 24 months and nerve conduction at 36 months [119]. Islet cell transplantation also improves nerve conduction velocity and amplitude scores [168]. This highlights the need for an adequate trial duration or more sensitive endpoints such as CCM for clinical trials of disease-modifying treatment for diabetic neuropathy.

Treatment based on pathogenetic concepts

Over the last 40 years we have witnessed the failure of multiple clinical trials of numerous pathogenetic treatments of diabetic sensorimotor polyneuropathy [169]. Although some drugs showed promising results in phase II trials, none made it past phase III to gain US Food and Drug Administration (FDA) approval as disease-modifying treatments for diabetic neuropathy [114, 170]. It is conceivable that drugs interfering with the pathogenesis of diabetic neuropathy may be most effective in early phases of the disease to prevent rather than reverse and repair nerves. Equally, the endpoints advocated by the FDA may not be sufficiently sensitive to detect nerve repair within the duration of most phase III trials lasting 12–24 months (Table 45.3).

Alpha-lipoic acid

Alpha-lipoic acid is an antioxidant and is claimed to be a disease-modifying therapy for diabetic neuropathy. However, it has never been approved by the FDA or endorsed by the ADA [1], as pivotal phase III studies failed to show efficacy in diabetic sensorimotor polyneuropathy [171]. A meta-analysis of all the major trials of alpha-lipoic acid including Symptomatic Diabetic Neuropathy (SYDNEY), Alpha-Lipoic Acid in Diabetic Neuropathy (ALADIN) I and II, and Neurological Assessment of Thioctic Acid in Diabetic Neuropathy (NATHAN) showed that 600 mg of intravenous alpha-lipoic acid over three weeks significantly improved neuropathic symptoms, but without long-term benefits on symptoms, quantitative sensory testing, or nerve conduction velocity [171].

Aldose reductase inhibitors

Increased aldose reductase enzyme activity causes an accumulation of sorbitol and fructose and aldose reductase inhibitors block the polyol pathway. Aldose reductase inhibitors have been tested in phase III clinical trials, but have not been approved by the FDA due to lack of efficacy or toxicity [172, 173]. Epalrestat is marketed in Japan and India based on the Aldose Reductase Inhibitor-Diabetes Complications Trial, which showed a delay in progression of diabetic neuropathy over three years in Japanese individuals with mild neuropathy [174]. Ranirestat showed a significant improvement in

Table 45.3 Treatment options for painful diabetic neuropathy.

Approach	Compound/measure	Dose per day	Remarks	NNT (95% CI)
Optimal glycaemic management	Behavioural modification, OAD, insulin	Individual adaptation	Target HbA_{1c} ≤6.5–7% (48–53 mmol/mol)	–
Pathogenesis-oriented treatment	α-Lipoic acid (thioctic acid)[a]	600 mg IV infusion	RCT duration 3 wk	6.3[b]
		600–1800 mg orally	FSP; RCT duration 4 yr	2.8–4.2[b]
	Actovegin[a]	2 g IV, 1.8 g orally	FSP; RCT duration 6 mo	8.3[b]
	Benfotiamine[a]	600 mg orally	FSP; RCT duration 6 wk	?
Symptomatic treatment	Tricyclic antidepressants			3.6 (3.0 to 4.4)
	Amitriptyline	(10–)25–150 mg	NNMH 15	
	Desipramine	(10–)25–150 mg	NNMH 24	
	Imipramine	(10–)25–150 mg	CRR	
	Clomipramine	(10–)25–150 mg	NNMH 8.7	
	Nortriptyline	(10–)25–150 mg		
	SNRIs			
	Duloxetine	60–120 mg	Effective dose 60 mg	6.4 (5.2 to 8.4)
	α2–δ ligands			
	Gabapentin	900–3600 mg	Long titration	7.2 (5.9 to 9.1)
	Pregabalin	300–600 mg	Dose-dependent effect	7.7 (6.5 to 9.4)
	Weak opioids			
	Tramadol	50–400 mg	NNMH 7.8	4.7 (3.6 to 6.7)
	Local treatment			
	Capsaicin (0.025%) cream	4 times a day topically	Max. duration 6–8 wk	5.7
	Capsaicin 8%	One time 179 mg topically	3 mo repeat intervals as needed	10.6 (7.4 to 18.8)
	Strong opioids			4.3 (3.4 to 5.8)
Pain resistant to standard pharmacotherapy	Oxycodone, tapentadol		Add-on treatment	
	Electrical spinal cord stimulation		Invasive, specialist required	

CI, confidence interval; CRR, concentration–response relationship; FSP, favourable safety profile; HbA_{1c}, glycated haemoglobin; IV, intravenous; NNT, number needed to treat; NNMH, number needed for major harm; OAD, oral anti-diabetes drug; RCT, randomized controlled trial; SNRIs, selective serotonin norepinephrine reuptake inhibitors.
[a]Available only in some countries.
[b]≥50% symptom relief after 3 and 5 wk.

summed motor nerve (peroneal, tibial, and median) conduction velocity over 36 months without a significant effect on sensory nerve function [173].

Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) has an adverse effect on retinopathy by inducing angiogenesis and macular oedema, but is also thought to be neuroprotective [175]. Quattrini et al. showed a reduction in VEGF associated with intraepidermal nerve fibre loss in skin biopsies from individuals with diabetic sensorimotor polyneuropathy [176]. A double-blind RCT of 50 individuals showed an improvement in neuropathic symptoms, but no improvement in quantitative sensory testing or nerve conduction [177].

Angiotensin-converting enzyme inhibitors and calcium channel blockers

Given that microangiopathy is associated with a reduction in nerve conduction velocity and loss of myelinated nerve fibres [178], we randomized normotensive individuals with mild diabetic sensorimotor polyneuropathy to trandolapril or placebo and showed a significant improvement in nerve conduction velocity, amplitude, and F-wave latency over 12 months [179]. Subsequently we also showed that candesartan improves endothelial function and myogenic tone of resistance vessels in people with type 2 diabetes [180]. The Delapril and Manidipine for Nephroprotection in Diabetes (DEMAND) trial randomized 140 individuals to a combination of manidipine and delapril, delapril alone, or placebo [181]. After three years the development of diabetic sensorimotor polyneuropathy was lowest in individuals on manidipine and delapril (23.5%) compared to delapril (28.9%) and placebo (38.6%). Furthermore, of 60 individuals with diabetic sensorimotor polyneuropathy at baseline, 33.3% showed regression of neuropathy in the manidipine and delapril group compared to 28.9% on delapril and 8.3% on placebo [181].

Treatment of painful diabetic neuropathy

Although tight glycaemic management may prevent the progression of diabetic neuropathy, there is no evidence that improved glycaemic levels improve pain in diabetic sensorimotor polyneuropathy. A therapy that achieves ~30–50% pain relief is considered to be moderately effective, while >50% pain relief is considered a good outcome [182]. A recent systematic review has concluded that duloxetine, venlafaxine, pregabalin, oxcarbazepine, tricyclic antidepressants, atypical opioids, and botulinum toxin were more effective than placebo for reliving neuropathic pain, but quality of

life was poorly reported, studies were short term, and the drugs had substantial dropout rates of ~10% [183].

The limited benefit of any one agent alone reflects the complex aetiology of neuropathic pain. There is increasing recognition that *one size does not fit all* and, rather than blindly trying different therapies until one works, we should consider better clinical phenotyping and targeted therapies [184]. Superficial clinical phenotyping in relation to symptomatology does not improve the response to therapy [185]. However, more detailed phenotyping using quantitative sensory testing has shown that individuals with an irritable nociceptor compared to a non-irritable nociceptor phenotype had a significantly greater response to oxcarbazepine and reduced the overall number needed to treat (NNT) from 6.9 to 3.9 [186]. In a smaller study the relative efficacy of 5% lignocaine was assessed in 15 individuals with irritable nociceptors and 25 individuals without irritable nociceptors; it showed a greater effect in those with irritable nociceptors, on pain paroxysms and deep aching pain [187]. Rate-dependent depression of the spinal H reflex has been suggested as a marker for spinal disinhibition in painful diabetic neuropathy [188]. This measure differentiates individuals with type 1 diabetes and painful diabetic neuropathy in relation to their response to duloxetine compared to pregabalin, potentially ushering in a personalized medicine approach in the treatment of painful diabetic neuropathy [189].

Neurological pathways implicated in mood disorders share neurotransmitters with pathways associated with pain processing [190]. It is therefore unsurprising that there is a dual utility in alleviating neuropathic pain.

Tricyclic antidepressants

Tricyclic antidepressants indirectly modulate the opioid system in the brain via serotonergic and norepinephrine neuromodulation, among other properties [191–193]. Tricyclic antidepressants require uptitration to effective doses, often over a period of 6–8 weeks before reasonable effects are noted, hence medication persistence may sometimes be compromised [194]. Tricyclic antidepressants remain first- or second-line therapies in all five international guidelines on pain management in diabetic sensorimotor polyneuropathy, with most citing amitriptyline as the tricyclic antidepressant of choice. A joint report on painful diabetic neuropathy from the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation concluded that amitriptyline has the greatest efficacy among tricyclic antidepressants [195]. There is currently insufficient evidence for the routine use of imipramine [196]. Tricyclic antidepressants are contraindicated in people with orthostatic hypotension, unstable angina, myocardial infarction within six months, heart failure, history of ventricular arrhythmias, significant conduction system disease, and long QT syndrome, and should be used with caution, particularly in older people [1].

Serotonin–norepinephrine reuptake inhibitors

Serotonin–norepinephrine reuptake inhibitors primarily exert their effect via inhibiting serotonin and norepinephrine reuptake resulting in the excitation of inhibitory descending pathways [197]. Duloxetine is approved by the FDA for the treatment of painful diabetic neuropathy and both 60 mg and 120 mg doses have been found to be effective [198], with a 50% pain reduction by 12 weeks (NNT = 5; 95% CI 4 to 9) [199]. Duloxetine has a superior safety profile compared to amitriptyline owing to the comparably lower rates of anticholinergic side effects. The most frequent side effects of duloxetine (60/120 mg/d) include nausea (16.7/27.4%), somnolence (20.2/28.3%), dizziness (9.6/23%), constipation (14.9/10.6%), dry mouth (7.1/15%), and reduced appetite (2.6/12.4%). A *post hoc* analysis of three pooled double-blind, placebo-controlled trials evaluating the use of duloxetine in older individuals (aged >65 years) showed good safety and efficacy [200]. Venlafaxine has shown efficacy in painful diabetic neuropathy (NNT 3.1) with superiority to duloxetine in some studies, but there is a lack of larger trials showing this effect [201–203]. It is not approved by the FDA for the treatment of diabetic neuropathy. Desvenlafaxine has shown efficacy in a single RCT [204].

Anticonvulsants

Carbamazepine has been widely used for many years in the treatment of neuropathic pain, especially in the management of trigeminal neuralgia. However, Cochrane reviews of carbamazepine [205] and oxcarbazepine have shown limited efficacy in painful diabetic sensorimotor polyneuropathy [206]. There is also limited evidence to support the use of topiramate [207], lamotrigine [208–210], or lacosamide [210, 211] in painful diabetic neuropathy.

Alpha 2 delta ligands

Gabapentin is a lipophilic analogue of gamma-aminobutyric acid (GABA) that binds to the α-2/δ-1 subunit of the voltage-gated calcium channel on the presynaptic membrane and reduces excitability of chiefly glutaminergic neurones [212]. A significant improvement in pain scores can be seen eight weeks after starting gabapentin [213]. A systematic review of 35 studies in 727 individuals with neuropathic pain found that gabapentin was effective in alleviating pain, but its effectiveness was questionable at the low doses (300 mg twice a day) that are commonly prescribed [214]. There is a reasonable balance between safety and efficacy for the treatment of painful diabetic neuropathy [215].

Pregabalin, another analogue of GABA, has higher potency and FDA approval based on several RCTs showing efficacy in the treatment of painful diabetic neuropathy [216–218]. Somnolence is a common side effect of pregabalin, although in healthy volunteers it enhances slow-wave sleep, which is deep sleep and associated with consolidation of memory. Pregabalin improves subjective sleep and quality of life in individuals with painful diabetic neuropathy [219–221]. Side effects include oedema and mood disturbance and sudden discontinuation have been linked to the development of seizures, cerebral oedema, and encephalopathy [222].

Opioid analgesia

Tramadol is a centrally acting synthetic non-selective agonist with affinity at Mu, Delta, and Kappa opioid receptors, preferential for the Mu receptor, and also inhibits norepinephrine and serotonin reuptake [223]. The efficacy of tramadol in neuropathic pain has been determined in small, largely inadequate studies with a potential risk of bias [223]. A meta-analysis showed an NNT of 4.4 (95% CI 2.9 to 8.9) for 50% pain reduction, but it concluded that there were insufficient data of adequate quality to endorse tramadol as an effective therapy for neuropathic pain [223].

Tapentadol is a novel, centrally active analgesic with a dual mode of action: Mu-opioid receptor agonist and norepinephrine reuptake inhibitor. A 12-week open-label study demonstrated a 30% pain reduction in 65% of the individuals examined and a 50% pain reduction in 34.9% of enrolled individuals [224]. These findings

were confirmed in a 12-week study, leading to FDA approval in 2012, of modified-release tapentadol for the treatment of neuropathic pain [225].

Topical medications

The use of topical treatments may be particularly useful for persons who cannot tolerate systemic therapies due to adverse effects [226]. Furthermore, the risk of drug–drug interactions is also significantly reduced, making topical therapies more attractive for a growing number of individuals with multiple comorbidities and polypharmacy.

Capsaicin

Capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide) is a selective transient receptor potential vanilloid 1 (TRPV1) agonist, which is expressed on small nerve fibres. The activation of TRPV1 and release with depletion of substance P are claimed to reduce peripheral painful stimuli [227, 228]. A double-blind placebo-controlled trial using 0.0075% topical capsaicin found a significant reduction in pain as measured by physicians' global evaluation and visual analogue scales [229]. However, the use of topical capsaicin is limited by the frequency of application (four times daily) and burning pain frequently induced on application. It is of concern that a topical capsaicin patch increases thermal thresholds and reduces IENFD, with total denervation in some cases, which could increase the risk of diabetic foot ulceration [230].

Capsaicin is currently recommended as third-line therapy by the UK National Institute for Health and Care Excellence and as second-line therapy by the American Academy of Neurology for the treatment of neuropathic pain. In a 12-week double-blind trial in individuals with painful diabetic neuropathy, the 8% capsaicin patch improved both pain and sleep quality significantly [231]. In a 52-week RCT, up to seven consecutive 30-minute treatments with the 8% capsaicin patch as add-on to standard care was associated with sustained pain relief without apparent adverse effects on sensory function. In July 2021, the FDA approved the 8% capsaicin patch for the treatment of painful diabetic neuropathy.

Lidocaine

Lidocaine plasters (5%) applied for 18 hours per day provide effective relief in painful diabetic neuropathy. A systematic review of 38 studies found significant pain reduction using the 5% lidocaine patch, comparable to amitriptyline, capsaicin, gabapentin, and pregabalin [226]. The lidocaine patch is associated with fewer and less clinically significant side effects compared to systemic agents [226].

Isosorbide dinitrate

Impaired nitric oxide (NO) synthesis plays a role in the pathogenesis of diabetic neuropathy. Nitroglycerin releases NO, suggesting a potential role for people with diabetic neuropathy [161]. Additionally, the release of neuronal NO synthase in dorsal root ganglion cells and the spinal cord may contribute to spinal sensory processing and neuronal plasticity with pain relief [232]. A small double-blind trial (n = 22) found a significant reduction in pain intensity [233]. A further case series (n = 18) reported that individuals treated with glyceryl-trinitrate (GTN) patches showed a reduction in pain scores [234]. Topical lidocaine and GTN patches may be used in combination to provide 24-hour pain cover with alternating 12-hour application of each therapy.

Intravenous lidocaine

Intravenous lidocaine has been used for many years in the treatment of pain produced by nerve injury. Intravenous novocaine was used successfully to provide analgesia to burns individuals as early as 1943 [235]. Lidocaine modifies sodium channel expression, reducing peripheral nociceptive sensitization [236], and possesses anti-inflammatory properties equivalent to traditional anti-inflammatory drugs [237]. Inflammatory cytokines play a role in secondary hyperalgesia and the sensitization of the central nervous system to inappropriate pain signals [238]. A small double-blind placebo-controlled trial in 15 individuals with intractable painful diabetic neuropathy, refractory to standard treatment, showed significant analgesic effect with an intravenous lidocaine infusion that persisted for up to 28 days, without significant side effects [239].

Combination therapy

The response rates to analgesic monotherapy in painful diabetic neuropathy are limited. Combination pharmacotherapy is required in individuals who have only partial response or in whom the drug cannot be further titrated owing to intolerable side effects. In some trials, combined treatment showed superiority over monotherapy, but in others improved benefit or tolerability was not seen [240].

The only two medications with both FDA and European Medicines Agency approval for the treatment of painful diabetic neuropathy are pregabalin and duloxetine. The Combination vs Monotherapy of pregaBalin and dulOxetine in Diabetic Neuropathy (COMBO-DN) study was a multinational randomized double-blind, parallel-group trial designed to compare the efficacy and tolerability of high-dose monotherapy to standard-dose combination therapy with both pregabalin and duloxetine in individuals with painful diabetic neuropathy, with a limited response to standard-dose monotherapy [241]. There was no significant difference in the Brief Pain Inventory (BPI) score between the standard-dose combination therapy and high-dose monotherapy in those who did not achieve adequate pain relief on standard-dose duloxetine or pregabalin [241]. An exploratory *post hoc* analysis showed that high-dose monotherapy was more efficacious in individuals with severe pain, while combination therapy was more beneficial in those with moderate and mild pain [242]. Furthermore, the individuals who received duloxetine (60 mg/d) as initial therapy had a better response to combined duloxetine and pregabalin for evoked or severe tightness, but a greater benefit for paraesthesia or dysaesthesia with high-dose (120 mg/day) duloxetine [242, 243].

Non-invasive neuromodulation

A recent systematic review and meta-analysis assessed the potential benefits of non-invasive neuromodulation in 20 trials (18 RCTs and 2 quasi-experiments) with 1167 people with diabetes. There was a significant reduction in pain scores with central (effect size [ES] −0.75, 95% CI −1.35 to −0.14), but not peripheral techniques (electrical and electromagnetic; ES −0.58, 95% CI −1.23 to 0.07) [244].

Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation (TENS) modulates afferent transmission, increases the nociceptive flexion reflex threshold, and changes somatosensory evoked potentials. Individuals with painful diabetic neuropathy were treated three times weekly with micro-TENS therapy or placebo over four weeks and showed no significant difference in the percentage of individuals with >30% pain relief (micro-TENS 23% vs placebo 25%) [245]. Acupuncture-like

TENS and traditional TENS showed no significant reduction in individuals with painful diabetic neuropathy [246].

Percutaneous electrical nerve stimulation
Percutaneous electrical nerve stimulation (PENS) is an electroanalgesic therapy that combines the benefits of TENS and electroacupuncture and works by placing acupuncture-like needles in the skin to stimulate sensory nerves in the region of neuropathic pain. The only prospective crossover sham-controlled study is now over 20 years old and showed that over three weeks PENS provided short-term relief of pain and improved mood and physical activity, while reducing the need for oral analgesics [247].

Frequency-modulated electromagnetic neural stimulation
The frequency-modulated electromagnetic neural stimulation (FREMS) technique stems from the TENS family, but has a more distinct and novel mechanism of action with the delivery of a sequence of stimuli, which vary automatically in terms of pulse frequency, duration, and voltage amplitude. In a randomized study of individuals with painful diabetic neuropathy, FREMS was associated with a significant reduction in day and night pain immediately after each treatment session, and an improvement in cold sensation threshold with no change in vibration and warm sensation thresholds or nerve conduction velocity [248].

Electrical spinal cord stimulation
A systematic review comparing medical therapy with tonic spinal cord stimulation and dorsal root ganglion stimulation showed an improvement in pain after 12 months by 56% (95% CI 39 to 73) and 55% (96% CI 22 to 87), respectively. The rate of failed therapeutic stimulation was 16%, infection at the site of insertion was 4%, and problems with the lead requiring corrective surgery was 4% per year [249].

Low-intensity laser therapy
This technique is postulated to work by increasing the release of serotonin and endorphins and may have an anti-inflammatory effect. In a randomized, double-masked, sham therapy-controlled trial in 50 individuals with painful diabetic neuropathy, both groups showed a decrease in weekly mean pain scores, with the laser therapy group showing an additional non-significant reduction in weekly mean pain scores, but no effect on the Toronto Clinical Neuropathy Score, nerve conduction studies, sympathetic skin response, or quantitative sensory testing [250]. A recent study has shown an improvement in the healing of foot ulcers [251].

Acupuncture
Acupuncture involves the insertion of fine needles into the skin of predefined areas with stimulation of sensory nerves leading to pain relief. In a study comparing dragon-tiger fighting needling therapy to pregabalin 75 mg twice daily over two weeks, needling therapy showed a significant improvement in painful symptoms, quality of life, and, surprisingly, nerve conduction velocity [252]. In a recent systematic review that included 10 studies (three RCTs, two pilot RCTs, three uncontrolled clinical trials, one quasi-RCT, and one prospective case series) and 432 participants, there was an improvement in painful symptoms, but the risk of bias was high or unclear in the majority of studies [253].

Emerging therapies for painful diabetic sensorimotor polyneuropathy
Many putative treatments for diabetic neuropathy have failed in phase III trials. However, there are emerging treatments that may shift the pharmacological paradigm in the treatment of neuropathic pain.

Dextromethorphan
Dextromethorphan is a *N-methyl-D-aspartate* (NMDA) receptor antagonist and serotonin reuptake inhibitor. When administered as monotherapy, dextromethorphan has limited bioavailability due to rapid catabolism by hepatic cytochrome P4502D6, and therefore must be administered with a potent P4502D6 inhibitor such as quinidine. Shaibani et al. evaluated two doses of dextromethorphan/quinidine (DMQ) 45/30 mg or DMQ 30/30 mg in a double-blind placebo-controlled trial (n = 379) and showed that DMQ was significantly superior to placebo with a reasonable safety profile [254].

EMA401
EMA401 is a highly selective angiotensin II type 2 receptor antagonist. A phase 2 multicentre placebo-controlled double-blind trial in 183 individuals with post-herpetic neuralgia showed a significant reduction in a 11-point numerical rating scale with EMA401 (100 mg twice daily) over 28 days [255]. Two phase 2b multicentre, randomized, double-blind studies of EMA401 in people with post-herpetic neuralgia (EMPHENE; randomized 1 : 1 : 1 to either placebo, EMA401 25 mg, or EMA401 100 mg twice daily) and painful diabetic neuropathy (EMPADINE; randomized 1 : 1 to placebo or EMA401 100 mg twice daily) have demonstrated a non-significant reduction in pain score over 12 weeks [256]. However, both studies were prematurely terminated due to pre-clinical hepatotoxicity with long-term dosing observed in other ongoing studies and only enrolled 129/360 (EMPHENE) and 137/400 (EMPADINE) participants.

Cibinetide
Cibinetide is a non-haematopoietic peptide of erythropoietin that interacts selectively with the innate repair receptor mediating tissue protection [257], as well as being an antagonist of the TRPV1 receptor [258], mediating a disease-modifying and analgesic effect, respectively. In two phase 2b studies it led to a significant reduction in painful neuropathy scores and small nerve fibre regeneration in the cornea and skin in individuals with diabetic painful neuropathy [259] and sarcoid neuropathy [260].

Tanezumab
Tanezumab is the first fully humanized monoclonal antibody that binds circulating and tissue nerve growth factor (NGF), preventing it from binding to tropomyosin receptor kinase A and p75 and reducing the expression of pain-related transmitters, receptors, and ion channels. However, in 2010 an FDA hold was placed on anti-NGF mAb clinical studies, because of reports of serious joint-related adverse events and concerns of sympathetic nerve damage. Therefore, to date there is only one report from a prematurely terminated clinical trial reporting after eight weeks. Individuals with diabetic painful neuropathy were randomized to subcutaneous tanezumab 20 mg administered on day 1 and week 8 (n = 38) or placebo (n = 35). There was a significant reduction in the average pain score and significantly higher percentages of tanezumab-treated individuals had ≥30%, ≥50%, and ≥70% reductions in average pain

scores at week 4 and week 8, with no change in the neuropathy impairment score and quantitative sensory testing, though there was a non-significant reduction in IENFD [261]. In 2017 the FDA granted fast-track status for tanezumab as a non-opioid pain medication, particularly for hip and knee osteoarthritis, and trials are also being currently undertaken for neuropathic pain.

Vitamin D

Vitamin D deficiency is highly prevalent in people with diabetes and is a risk factor for diabetic sensorimotor polyneuropathy [262, 263]. A meta-analysis in people with type 2 diabetes (n = 1484) confirmed a highly significant correlation between serum vitamin D3 levels and the risk of diabetic neuropathy [264]. We have shown that vitamin D deficiency is particularly associated with painful diabetic neuropathy and the odds ratio in favour of painful diabetic neuropathy was 9.8 (95% CI 2.2 to 76.4) for vitamin D deficiency (<20 µg/l) and 4.4 (95% CI 1.1 to 19.8) for vitamin D insufficiency (<30 µg/l) [265]. In an open-label prospective study, a single intramuscular dose of 600 000 IU of vitamin D3 provided significant pain relief in a cohort of individuals with painful diabetic neuropathy [266].

Diabetic autonomic neuropathy

Cardiac autonomic neuropathy

Cardiac autonomic neuropathy is the impairment of cardiovascular autonomic control in people with diabetes after the exclusion of other causes [267]. Abnormal cardiovascular autonomic reflex tests have been reported in up to 7% of individuals at diagnosis of type 1 diabetes and type 2 diabetes [268–270], with an increase in prevalence to 30% (DCCT/EDIC) after 14 years of type 1 diabetes [148, 271] and in other studies to 70% after 15 years [272].

Cardiac autonomic neuropathy is an independent risk factor for mortality in people with diabetes [267, 273]. A meta-analysis of 12 studies (n = 1468) showed that individuals with cardiac autonomic neuropathy have a 1.96-fold (95% CI 1.53 to 2.51) increased risk of silent myocardial ischaemia during exercise [108] and it is also associated with left ventricular dysfunction [274, 275]. Cardiac autonomic neuropathy extends cardiovascular risk stratification in people with and without cardiovascular disease and identifies individuals requiring more intensive monitoring during the perioperative period.

Diagnosis of cardiac autonomic neuropathy

The ADA recommends screening for cardiac autonomic neuropathy at diagnosis of type 2 diabetes and after five years for those with type 1 diabetes. Furthermore, individuals with microvascular complications and hypoglycaemia unawareness should be assessed for cardiac autonomic neuropathy [1, 276]. The diagnosis of cardiac autonomic neuropathy includes the documentation of symptoms and signs (Table 45.4), although there is a weak correlation between symptoms and autonomic deficits [272, 277]. Cardiac autonomic neuropathy may initially be asymptomatic, with the only sign being decreased heart rate variability with deep breathing, which can progress to a resting tachycardia (>100 bpm). In individuals with resting tachycardia and a history of suboptimal glucose management, where the diagnosis of cardiac autonomic neuropathy is very likely, the ADA position statement advises no additional testing [1]. It is important to exclude other causes such as idiopathic orthostatic hypotension, syncope, and postural orthostatic tachycardia syndrome [278].

Table 45.4 Clinical manifestations of diabetic autonomic neuropathy.

System	Manifestation
Cardiovascular system	Resting tachycardia, orthostatic hypotension
	Sudden death, malignant arrhythmia
Respiratory system	Reduced ventilatory drive to hypercapnia/hypoxaemia
	Sleep apnoea, respiratory arrest
Pupillary system	Pupillary reflex dysfunction, reduced dark adaptation
Gastrointestinal tract	Oesophageal motor dysfunction
	Diabetic gastroparesis (gastropathy)
	Gallbladder dysfunction
	Diabetic enteropathy (diarrhoea)
	Colonic hypomotility (constipation)
	Anorectal dysfunction (faecal incontinence)
Urogenital system	Diabetic cystopathy (neurogenic vesical dysfunction)
	Erectile dysfunction, female sexual dysfunction
Thermoregulation	Sudomotor dysfunction: distal hypohydrosis or anhidrosis, gustatory sweating
	Vasomotor dysfunction: vasodilatation, arteriovenous shunting, peripheral oedema
Neuroendocrine system	Hypoglycaemia-associated autonomic failure (HAAF)
	Defective counter-regulation, hypoglycaemia unawareness
	Reduced hormonal responses to orthostatic changes/exercise

Cardiovascular autonomic reflex testing

Cardiovascular autonomic reflex testing are the gold standard for diagnosing cardiac autonomic dysfunction. They are well standardized and easily performed with good sensitivity, specificity, and reproducibility, but are not widely available [279]. The diagnosis of cardiac autonomic neuropathy should be based on an abnormality in at least two of the following cardiac autonomic tests as per the Ewing criteria [267]:

- Parasympathetic function:
  - Heart rate response to deep breathing (excitation/inhibition [E/I] ratio).
  - Heart rate response to standing (30 second/15 second ratio).
  - Heart rate response to the Valsalva manoeuvre (Valsalva ratio).
- Sympathetic function:
  - Blood pressure response lying to standing.
  - Blood pressure response to a sustained handgrip.

A complete diagnostic work-up for cardiac autonomic neuropathy is presented in Table 45.5. Heart rate variability can be assessed by calculation of indices based on the R–R interval (time domain analysis) or by spectral analysis (frequency domain analysis) of an array of R–R intervals on an electrocardiogram (ECG). The Valsalva manoeuvre should not be performed in those with advanced diabetic retinopathy because of the potential risk of inducing retinal or vitreous haemorrhage.

The Toronto Neuropathy Study Group recommends that the diagnosis of cardiac autonomic neuropathy is based on at least one abnormality in heart rate response to deep breathing, standing, and the Valsalva manoeuvre, and blood pressure response to standing with the following staging [34]:

- Possible or early cardiac autonomic neuropathy defined by the presence of one abnormal cardiovagal test.
- Definite or confirmed cardiac autonomic neuropathy defined by at least two abnormal cardiovagal tests.

Table 45.5 Diabetic autonomic neuropathy of the cardiovascular, respiratory, neuroendocrine, sudomotor, vasomotor, and pupillomotor systems: clinical features, diagnostic work-up, and specific treatment.

Organ manifestations/clinical features	Diagnostic procedures	Treatment
Cardiovascular system		
Resting tachycardia and/or fixed heart rate	Basic diagnostic work-up	Cardiovascular autonomic neuropathy
Loss of circadian rhythm of blood pressure	HRV during deep breathing and after standing	In general, no specific treatment necessary (diagnosis and therapy of coronary heart disease and heart failure)
Increase in nocturnal systolic blood pressure	Postural change in blood pressure	
Orthostatic hypotension		
Exercise intolerance	Extended diagnostic work-up	Sinus tachycardia: cardioselective β-receptor blockers
Abnormal plasma catecholamines	Cardiac autonomic function tests	
Syncope and light-headedness, visual impairment, and fragility	Resting HRV (time and frequency domain)	Orthostatic hypotension
	E/I ratio during deep breathing; max/min 30 : 15 ratio	Liberal salt intake, physical training, compression stockings, avoidance of hypotensive drugs
Intraoperative cardiovascular lability	Valsalva ratio	Midodrine (α_1-adrenergic agonist)
Silent ischaemia and painless myocardial infarction	Orthostatic test	Fludrocortisone
Diastolic dysfunction	24 h HRV, syncope work-up	(9α-fluorohydrocortisone)
Arrhythmias		
Sudden cardiac death		
Respiratory system		
Central respiratory dysregulation with reduced respiratory drive in response to hypercapnia or hypoxia	Sleep laboratory, as applicable	CPAP therapy, as applicable
Sleep apnoea syndrome		
Respiratory arrest		
Neuroendocrine system		
Hypoglycaemia-associated autonomic dysfunction	Optimal blood glucose management	Avoidance of symptomatic and asymptomatic (often nocturnal) hypoglycaemia
Blunted or absent hormonal counter-regulation		
Hypoglycaemia unawareness		Hypoglycaemia awareness training (blood glucose awareness training)
Increased glucose threshold for hypoglycaemic symptoms		
Decreased catecholamine secretion when standing or on physical exertion		
Sudomotor and vasomotor systems		
Dyshidrosis, anhidrosis ('dry feet')	Sweat tests	Topical agents containing fat or urea
Gustatory sweating	Quantitative sudomotor axon reflex test	Avoidance of exposure to intense heat
	Thermoregulatory sweat test	Limiting intake of identified cause of sweating (dietary component)
	Silastic sweat imprint	
	Acetylcholine sweatspot test	Anticholinergic drugs, clonidine (low dose)
	Neuropad: indicator plaster	Topical glycopyrrolate cream
	Sudoscan: quantitative sudomotor test	Focal hyperhidrosis: Botulinum toxin
Pupillomotor system		
Myosis Defective pupillary reflexes Reduced dark adaptation	Clinical examination	Advise patient of impaired adaptation to dark and danger of night blindness
	Infrared pupillography (constriction rate, dilation rate, latency of pupillary light reflex)	Glaucoma (check intraocular pressure)

CPAP, continuous positive airway pressure; E/I, expiration/inspiration; HRV, heart rate variability.
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• Severe or advanced cardiac autonomic neuropathy defined by orthostatic hypotension (asymptomatic or symptomatic), in addition to heart rate test abnormalities.

There is a circadian variation in the frequency of acute cardiovascular events, with an increased incidence in the hours of the early morning. It is therefore important to undertake 24-hour monitoring of heart rate and blood pressure when studying the neural control of the circulation [280].

Novel techniques for the diagnosis of cardiac autonomic neuropathy

CCM has been used to show that corneal nerve loss has a high diagnostic sensitivity and specificity for diabetic autonomic neuropathy [281] and sudomotor dysfunction [282]. Sudoscan measures foot and hand electrochemical skin conductance as a marker of sympathetic sudomotor dysfunction [141] shows a sensitivity of 65% and specificity of 80% for cardiac autonomic neuropathy [141, 283]. LDI FLARE closely correlates with heart rate variability in people with type 1 diabetes [284].

Management of cardiac autonomic neuropathy

Established risk factors for cardiac autonomic neuropathy include persistent hyperglycaemia, diabetes duration, hypertension, obesity, hyperlipidaemia, and smoking [148, 151, 270–272, 285–287]. The Steno-2 trial showed that intensified multifactorial treatment to improve weight, blood pressure, glycaemia, and lipids in people with type 2 diabetes reduced the risk of cardiac autonomic neuropathy progression by 68% [288, 289]. In the DCCT, intensive

glycaemic management in people with type 1 diabetes reduced the development of cardiac autonomic neuropathy by 45% [148]. There are currently no FDA-approved disease-modifying treatments to reverse cardiac autonomic neuropathy. A small study had suggested favourable effects of alpha-lipoic acid on cardiac autonomic neuropathy [290]; however, triple antioxidant therapy (allopurinol 300 mg daily, alpha-lipoic acid 600 mg twice daily, and nicotinamide 750 mg twice daily) in individuals with mild to moderate cardiac autonomic neuropathy found no benefit [291].

Orthostatic hypotension

Orthostatic hypotension is defined by a reduction in blood pressure on standing of >20/10 mmHg (in those with blood pressure >150/90 mmHg a fall of >30/15 mmHg) without an appropriate increase in heart rate (<15 bpm) [292]. The symptoms of orthostatic hypotension include light-headedness, weakness, faintness, and syncope. Management includes a review of medication, fluid and salt repletion, and encouragement of physical activity and exercise to avoid deconditioning [293, 294]. Midodrine and droxidopa are approved by the FDA for the treatment of symptomatic neurogenic orthostatic hypotension [295]. Fludrocortisone is not FDA approved, but works principally through sodium retention; however, there are concerns over supine hypertension, hypokalaemia, congestive cardiac failure, and peripheral oedema [296].

Gastrointestinal dysfunction

Gastrointestinal symptoms occur frequently among people with diabetes and are associated with considerable morbidity [297]. Autonomic neuropathy of the gastrointestinal system may involve the oesophagus, stomach, gallbladder, pancreas, and small and large intestine. The clinical features, diagnostic work-up, and specific treatment of diabetic autonomic neuropathy involving the gastrointestinal tract are listed in Table 45.6.

Oesophageal dysfunction

The prevalence of oesophageal dysmotility in people with diabetes is as high as 63% [298]. The thoracic oesophagus and lower oesophageal sphincter are composed of smooth muscle fibres innervated by the autonomic nerves of the myenteric plexus. Autonomic neuropathy and structural remodelling of the oesophageal musculature in diabetes result in abnormal peristalsis, spontaneous contractions, and reduced lower oesophageal sphincter tone [299]. Symptoms including dysphagia, retrosternal discomfort, and heartburn are uncommon and an obstructive lesion should be ruled out via endoscopy [276]. Oesophageal motility disturbances are demonstrable using scintigraphic techniques. Manometric studies show diminished pharyngeal and oesophageal contractions and reduced lower sphincter tone. Prokinetic drugs can be tried empirically. Since people with reduced oesophageal motility may be at risk of delayed transit and hold-up of tablets, potentially leading to localized mucosal ulceration and delayed drug absorption, they should always drink after taking their medication.

Gallbladder dysfunction

Autonomic neuropathy may lead to an atonic gallbladder that dilates with bile retention leading to stone formation [276].

Gastroparesis

Diabetes is the most common cause of gastroparesis, a condition characterized by delayed gastric emptying in the absence of a mechanical obstruction [300]. Gastroparesis can manifest with a variety of symptoms, including early satiety, nausea, vomiting, and anorexia. In more refractory cases it is associated with significant morbidity, impaired quality of life, anxiety, and depression having an impact on the individual's self-management of diabetes [301, 302].

Gastric emptying is determined by the physicochemical composition of food (carbohydrates leave the stomach most rapidly, proteins less so, and fats remain longest), its consistency (large chunks of meat remain in the stomach longer than small pieces), motor activity of the stomach, and the interaction of the stomach and duodenum, including involvement of gastrointestinal hormones. Gastric emptying is dependent on coordinated smooth muscle contraction regulated by the enteric neural plexus, and the intensity is controlled by efferent sympathetic and parasympathetic activity. Any abnormality of gastric electrical rhythm and transmission can lead to ineffective gastric propulsion [303, 304].

Diagnosis

The diagnosis of gastroparesis entails the exclusion of a mechanical obstruction, typically with an oesophagogastroduodenoscopy or barium meal. The gold standard for diagnosis of gastroparesis is gastric-emptying scintigraphy. This involves an overnight fast followed by a standard low-fat radiolabelled meal, ingested within 10 minutes. Imaging is performed at baseline and after one, two, and four hours in the standing position. Gastric delay is defined by >60% retention at two hours or >10% retention at four hours. A gastric-emptying breath test and SmartPill™ (Medtronic, Watford, UK) are alternative methods to establish gastric delay. The SmartPill enables ambulatory assessment of individuals, is radiation free, and may also provide additional physiological information [305].

Management

The general principles of management are to restore nutritional and hydration status, alleviate symptoms, and stabilize glucose levels [306]. Dietetic input should be sought early, with multiple small meals low in fat and fibre being preferred to fewer large ones [307–309]. Assisted nutrition should be considered when oral nutrition is not possible or inadequate and the enteral route is preferable to parenteral nutrition, due to the lower risk of complications such as line infection and thrombosis [309]. Optimization of insulin treatment with the use of basal insulin and omission or delay in the prandial injection can be useful. In an open-labelled pilot study of 42 individuals with gastroparesis (both type 1 diabetes and type 2 diabetes), there were improved glycaemic levels, less hypoglycaemia, and an improved gastroparesis symptom score with the use of sensor-augmented pump or pump and continuous glucose monitoring [310].

Metoclopramide is the only FDA-approved drug for the treatment of gastroparesis. However, concerns regarding potentially irreversible tardive dyskinesia have led to an FDA warning restricting its use to no longer than three months and recommendations to use the lowest effective dose for the shortest possible time. Domperidone is licensed only for treating nausea and vomiting and should be used at the lowest effective dose for the shortest possible duration, not exceeding one week. Erythromycin is a macrolide antibiotic that is an agonist of the motilin receptors leading to increased antral contraction [311]. The intravenous route is favoured in acutely hospitalized individuals, though tachyphylaxis may occur with this drug, usually after four weeks of use [312].

Mechanical options for intervention include transpyloric stenting, gastric electrical stimulation, and gastric per-oral endoscopic myotomy, and in severe intractable gastroparesis laparoscopic pyloroplasty or gastrectomy [306].

Table 45.6 Diabetic autonomic neuropathy of the gastrointestinal tract: clinical features, diagnostic work-up, and specific treatment.

Organ manifestations/clinical features	Diagnostic procedures	Treatment
All gastrointestinal manifestations	Basic diagnostic work-up History Exclusion of structural and infectious diseases	
Dysphagia and reflux disease	Extended diagnostic work-up Stage 1 Oesophagogastroduodenoscopy Other relevant imaging Stage 2 Oesophageal manometry 24 h pH monitoring	Dysphagia Prokinetic agents in individual cases Reflux Proton pump inhibitors
Diabetic gastroparesis	Stage 1 Oesophagogastroduodenoscopy Abdominal sonography Other imaging, as applicable Laboratory tests Stage 2 Gastric-emptying scintigraphy [^{13}C]Octanoic acid breath test	Gastroparesis Dietary change: frequent, small, low-fibre, low-fat meals Adjust insulin injection to meal interval Prokinetic agents: metoclopramide, domperidone Erythromycin (off-label) For severe refractory symptoms Gastric electrical stimulation (gastric pacemaker) Jejunal feeding tube Parenteral nutrition
Diabetic cholecystopathy	Laboratory tests Abdominal sonography	
Diabetic diarrhoea (enteropathy) and exocrine pancreatic insufficiency	Stage 1 Endoscopy Abdominal sonography Laboratory tests, including examination of stool for pathogenic organisms Other imaging, as applicable Stage 2 Lactose, fructose, sorbitol hydrogen breath test Glucose hydrogen breath test Faecal elastase-1, as applicable Lactulose hydrogen breath test, as applicable D-Xylose absorption test, as applicable	Diarrhoea Bulking agents Loperamide Cholestyramine Clonidine Octreotide Bacterial overgrowth of the small intestine Broad-spectrum antibiotics (e.g. ciprofloxacin, metronidazole, and doxycycline one after the other, each for 10 d) Severe exocrine pancreatic insufficiency Pancreatic enzymes
Diabetic constipation (colonic hypomotility)	Stage 1 Digital rectal examination Ileocolonoscopy Laboratory tests Abdominal sonography, as applicable Other imaging, as applicable Stage 2 Magnetic resonancing imaging (MRI) defecography Anorectal manometry Hinton test Neurological examination	Constipation Sufficient fluids, fibre, and physical activity Gelling agents (pectins, psyllium preparations) Fibre-rich foods, e.g. wheat bran, linseed Laxatives, e.g. sodium picosulfate, bisacodyl, macrogol, lactulose/lactitol Depending on tolerance and efficacy Biofeedback for rectal emptying disorder Prucalopride (licensed only in women)
Diabetic faecal incontinence	Stage 1 Digital rectal examination Rectal endosonography MRI defecography Stage 2 Anorectal manometry Neurological examination, as applicable	Faecal incontinence Anti-diarrhoeal medications Pelvic floor gymnastics Biofeedback Sacral nerve stimulation in refractory cases

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Diabetic diarrhoea

Diabetic diarrhoea is a troublesome gastrointestinal complication characterized by intermittent, brown, watery, painless, and voluminous stool, particularly at night. Other causes of diarrhoea must be excluded, especially concomitant metformin use and pancreatic exocrine insufficiency. Diarrhoea has been reported by up to 20% of people with diabetes [313]. Steatorrhoea is also common and may occur in as many as 75% of people with diabetic diarrhoea. Typically, diabetic diarrhoea occurs in long-standing and suboptimally managed type 1 diabetes and is more common in men than

in women. The pathogenesis is complex and autonomic neuropathy, bacterial overgrowth, and pancreatic exocrine insufficiency may all contribute [314]. If bacterial overgrowth is present, then broad-spectrum antibiotics should be the first step in management with courses of 1–2 weeks every month. Other pharmacological therapies include somatostatin analogues (octreotide) and selective serotonin 5-hydroxy tryptamine type 3 (HT3) receptor antagonists (ramosetron) [314, 315].

Colonic dysfunction

Constipation may affect ~60% of people with type 2 diabetes and is a common gastrointestinal complaint, although it may also be attributed to ageing [313]. Increased oxidative stress and apoptosis with loss of enteric neurons contribute to the motility disturbances [316]. The diagnostic assessment includes a digital rectal examination, proctosigmoidoscopy, and/or colonoscopy. Megacolon or megasigmoid may be found occasionally. Symptoms do not correlate with radiographic changes, which may be absent despite significant symptoms. The colonic segmental transit time can be examined using radiopaque markers to distinguish between diffuse colonic hypomotility and rectosigmoid dysfunction [317].

An increase in dietary fibre may reduce the intestinal transit time. However, it may also lead to increased gas production and the quantity of fibre should be increased gradually to avoid excessive flatulence and bloating, which may already be present in people with diabetes. Lactulose decreases pH and increases osmotic activity to stimulate colonic propulsive activity. Chronic laxative use, particularly with the anthraquinone group (senna, cascara, aloes), may aggravate existing autonomic neuropathy. More severe constipation or obstipation unresponsive to conventional management may benefit from a trial of drugs that stimulate the colonic smooth muscle, including bethanechol (cholinergic agonist) or pyridostigmine (cholinesterase inhibitor) [317].

Urogenital system

Bladder dysfunction

Bladder dysfunction may occur in up to 50% of individuals with diabetes [278] and presents with a spectrum of symptoms ranging from bladder overactivity to impaired bladder contractility and urinary retention [318]. The *temporal theory of diabetic bladder dysfunction* proposes that hyperglycaemia-induced polyuria causes compensatory bladder hypertrophy and associated myogenic and neurogenic alterations [319]. Diabetic cystopathy begins with an increased initiating threshold for the micturition reflex, followed by decreased detrusor activity and incomplete bladder emptying [320]. People with mild autonomic neuropathy initially report reduced urinary frequency; however, as autonomic efferent fibres become damaged, the frequency of urination declines and dribbling and overflow incontinence ensue. It is important to exclude other conditions such as urinary tract infection, and therefore urinalysis and culture and examination for benign prostatic hypertrophy are important, especially in older men. In women, it is important to include a complete urogynaecological examination to rule out pelvic organ prolapse, as well as an assessment of the integrity of pelvic floor muscle.

Urodynamic evaluation should be performed to differentiate between people with diabetic cystopathy and other causes of bladder outflow obstruction. Cystometry usually shows the presence of residual urine and reduced sensation of bladder filling. A study of 194 women with type 2 diabetes showed that they had significantly higher nocturia scores, weaker urinary streams, reduced voided volumes, and an increased residual urine volume of >100 ml in 13.9% compared to 1.8% of women without diabetes [321]. Over time the progressive increase in post-void residual volume can lead to chronic urinary tract infection and irreversible bladder fibrosis, with hydroureteronephrosis and renal impairment. The clinical features, diagnostic work-up, and specific treatment of diabetic autonomic neuropathy of the urogenital system are shown in Table 45.7.

Management

Therapies include lifestyle modification such as weight reduction, amount and timing of fluid intake, and pelvic floor muscle training. Individuals should be educated to void every third hour during the daytime to compensate for the lack of first desire to void. Repetitive voiding by double or triple voiding techniques may replace deficient detrusor contraction and enable the person to discharge almost all of the bladder volume. Crede's manual compression to apply suprapubic pressure or the Valsalva manoeuvre can also be useful in facilitating micturition [322]. However, in people with impaired or absent detrusor muscle activity, intermittent self-catheterization is the primary therapy [323].

Anti-cholinergic drugs may benefit those with detrusor overactivity; however, there is a limited role for pharmacotherapy in the treatment of detrusor areflexia. Antimuscarinic medication includes oxybutynin 5–30 mg three times a day and tolterodine 2–8 mg twice a day for detrusor hyperreflexia and parasympathomimetic medication to reduce detrusor contractility [1]. Surgical options for individuals with refractory symptoms include vesical neck resection, though this carries a risk of retrograde ejaculation in men and cystourethrocele in women [324]. Selective pudendal nerve block may be used to reduce bladder outlet resistance and sacral neuromodulation.

Erectile dysfunction

Sexual function in men and women with diabetes is discussed in greater detail in Chapter 54 and so will only be covered in brief here. Erectile dysfunction is defined by the persistent or recurrent inability to achieve and maintain penile erection of sufficient rigidity to permit satisfactory sexual activity for at least three months [325]. It occurs in ~50% of men with diabetes and is more severe and less responsive to treatment compared to men without diabetes [326]. Risk factors include persistent hyperglycaemia, metabolic syndrome, hypertension, dyslipidaemia, lower estimated glomerular filtration rate (eGFR), and higher albumin-to-creatinine ratio.

Cholinergic and non-cholinergic non-adrenergic neurotransmitters mediate erectile function by relaxing the smooth muscle of the corpus cavernosum. A principal neural mediator is NO, which activates guanyl cyclase to form intracellular guanosine monophosphate, a potent second messenger for smooth muscle relaxation. *In vivo* studies of isolated corpus cavernosum tissue from men with diabetes have shown functional impairment in autonomic and endothelium-dependent relaxation of corpus cavernosum smooth muscle [327, 328]. Small nerve fibre damage detected using CCM is more closely associated with erectile dysfunction than testosterone levels in men with type 1 diabetes [329], type 2 diabetes [330], and obesity [331].

The aim of initial management is to encourage smoking and alcohol cessation, reduce weight and metabolic syndrome [332], and treat with statins [333]. Treatment with testosterone is recommended in individuals with low testosterone levels (<8 nmol/l; 231 ng/dl) and reduced libido, but is contraindicated in men with prostate or breast cancer or severe heart failure [334].

Table 45.7 Diabetic autonomic neuropathy of the urogenital system: clinical features, diagnostic work-up, and specific treatment.

Organ manifestations/ clinical features	Diagnostic procedures	Treatment
Diabetic cystopathy (bladder-emptying dysfunction)	Basic diagnostic work-up	Behavioural changes
	Micturition diary over 48 h	Electrical stimulation
	Extended diagnostic work-up	Biofeedback
	International Prostate Symptom Score (IPSS)	Anticholinergics
	Uroflowmetry	α-Receptor blockers
	Residual urine measurement	Antibiotic therapy
	Digital rectal examination for men	Bladder neck incision
	Urodynamic testing	Self-catheterization
		Suprapubic cystostomy
Erectile dysfunction	Basic diagnostic work-up	Erectile dysfunction
		Avoidance of medication leading to (antihypertensives, antidepressants)
	Stage 1	Stage 1
	Sexual history, International Index of Erectile Function questionnaire (IIEF-5)	PDE-5 inhibitors (sildenafil, tadalafil, vardenafil)
	Total (free) testosterone, prolactin, FSH, LH	
	Stage 2 (optional)	Stage 2
	Test with a PDE-5 inhibitor (sildenafil, vardenafil, tadalafil)	Erection aid system (vacuum pump)
		Corpus cavernosum auto-injection therapy
	Extended diagnostic work-up	
	Stage 3 (only if surgical therapy is planned/indicated)	Stage 3
	Intracavernosal injection test	Corpus cavernosum implant
	Doppler/duplex sonography	Hypogonadism
	Cavernosometry/cavernosography	Testosterone substitution
	Nocturnal tumescence measurement	

FSH, follicular stimulating hormone; LH, luteinizing hormone; PDE-5: phosphodiesterase type 5.
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The first-line oral medication is 5-phosphodiesterase (PDE-5) inhibitors. In a meta-analysis of starting dosages of PDE-5 inhibitors, sildenafil 50 mg had the greatest efficacy, but also had the highest rate of overall adverse events. Tadalafil 10 mg had intermediate efficacy, but had the lowest overall rate of all adverse events. Vardenafil 10 mg had similar overall adverse events to sildenafil 50 mg, but a markedly lower global efficacy [335]. Men with diabetes are less likely to respond to PDE-5 inhibitors, with a ~50% non-responder rate [336]. The lack of response may reflect a more severe neurogenic component in these individuals [329]. In a recent study the assessment of nocturnal penile tumescence and rigidity, which reflects predominantly neurogenic abnormalities, had an area under the curve (AUC) of 0.860 in differentiating sildenafil responders from non-responders [337]. Additional modalities such as low-intensity extracorporeal shock-wave therapy show promise [338–341], but require larger and better-designed clinical trials.

Female sexual dysfunction

Sexual dysfunction is more common in women with diabetes and almost one in two women with diabetic neuropathy reported sexual dysfunction [342]. Reduced sexual arousal, decreased lubrication, and painful intercourse are the most common symptoms of sexual dysfunction in women with diabetes. They are attributed to psychological factors more so than in men [343] and are also associated with depression [344, 345].

Gustatory sweating

Gustatory sweating refers to facial diaphoresis, often accompanied by flushing, that follows the ingestion of food or drink. It occurs particularly in individuals with diabetic nephropathy or neuropathy [346] and in one study 69% of individuals with nephropathy and 36% with neuropathy reported gustatory sweating, compared to less than 5% in people with diabetes without complications [347].

A double-blind placebo-controlled trial using a 0.5% glycopyrrolate cream applied to affected areas on alternate days showed a reduction in both the severity and frequency of diabetic gustatory sweating [346]. However, this agent is limited to those who do not experience scalp sweating, as it cannot be applied beyond the hairline. Intracutaneous injection of botulinum toxin type A in the affected facial skin area resulted in a cessation of sweating within four days and lasted for 24 weeks [348].

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8 Macrovascular Complications in Diabetes

46 Pathogenesis of Macrovascular Complications in Diabetes

Jakob A. Østergaard[1,2], Tomasz J. Block[1], Sophia Dahm[1], Waheed Khan[1], and Karin A.M. Jandeleit-Dahm[1,3]

[1] Department of Diabetes, Central Clinical School, Monash University, Melbourne, Victoria, Australia
[2] Steno Diabetes Center Aarhus and Department of Endocrinology & Internal Medicine, Aarhus University Hospital, Aarhus, Denmark
[3] German Diabetes Centre (DDZ), Institute for Clinical Diabetology, Leibniz Centre for Diabetes Research at Heinrich Heine University, Düsseldorf, Germany

Key points

- Diabetes accounts for 75–90% of excess coronary artery disease risk seen in people with diabetes and enhances the effects of other cardiovascular risk factors.
- A range of haemodynamic and metabolic factors contribute to macrovascular disease in diabetes.
- There is clear *in vitro* and *in vivo* evidence that glucose exerts direct and indirect toxic effects on the vasculature.
- The accumulation of advanced glycation end-products (AGEs) exerts pro-oxidant, pro-inflammatory, and pro-fibrotic effects on the vasculature via receptor-independent and receptor-dependent effects. Furthermore, the AGE receptor (RAGE) is pivotally involved in the pathogenesis of diabetes-accelerated atherosclerosis. The pro-inflammatory signalling of RAGE is mediated through the angiotensin II receptor type 1 (AT_1).
- Specific insulin resistance pathways appear to contribute to atherogenesis in diabetes.
- The components of the classic renin–angiotensin–aldosterone system (RAAS) and in particular more recently discovered components such as angiotensin-converting enzyme 2 appear to contribute to macrovascular disease in diabetes. Inhibitors of RAAS have consistently demonstrated reduced endothelial dysfunction and atherosclerosis in animal models via suppression of inflammation, fibrosis, and oxidative stress.
- Other vasoactive components such as endothelin and urotensin II are also likely to contribute to macrovascular complications in diabetes and interact with the RAAS. Furthermore, the role of novel tumour necrosis factor (TNF)-related ligands, such as TNF-related apoptosis-inducing ligand and osteoprotegerin, and the complement system in atherosclerosis are currently under evaluation.
- Treatments that reduce oxidative stress, including nicotinamide adenine dinucleotide phosphate (NADPH) oxidase inhibitors and inhibitors that attenuate inflammation, have been shown to be anti-atherosclerotic in experimental and clinical studies, although this effect is not uniform. Inflammasome activation plays an important role in diabetes-associated atherosclerosis.
- A multifactorial approach treating conventional cardiovascular risk factors in addition to diabetes-specific risk factors is currently viewed as the optimal strategy to reduce the burden of cardiovascular disease in diabetes.

Epidemiology of diabetic macrovascular complications

Macrovascular complications develop in people with type 1 diabetes [1, 2] and type 2 diabetes [3, 4]. This is of particular concern as the increasing prevalence of diabetes now also affects adolescents and younger adults, thus promoting the earlier development of long-term cardiovascular complications. Even after adjusting for concomitant risk factors, such as hypertension and hyperlipidaemia, there remains an excess risk for cardiovascular disease (CVD) in people with diabetes [5, 6]. Indeed, diabetes itself accounts for 75–90% of the excess coronary artery disease risk and enhances the effects of other cardiovascular risk factors. Death from stroke and from myocardial infarction are leading causes of mortality in type 1 diabetes and type 2 diabetes [2, 7].

A range of haemodynamic and metabolic factors have been considered responsible for the development and progression of macrovascular disease in diabetes (Figure 46.1) [8]. In terms of haemodynamic factors, the hormonal cascade known as the renin–angiotensin–aldosterone system (RAAS) plays a pivotal role in diabetes-associated atherosclerosis; however, other vasoactive hormone systems, such as the endothelin [9] and urotensin systems [10, 11], have also been implicated in diabetes-related macrovascular disease. Furthermore, oxidative stress and a decrease in antioxidant defence have emerged as critical factors driving many atherogenic processes in diabetes [12], in addition to a host of immune-inflammatory responses involving factors such as tumour necrosis factor (TNF)–related apoptosis-inducing ligand (TRAIL) [13] and the complement system [14]. More recently, activation of the inflammasome has also been shown to contribute to CVD in diabetes.

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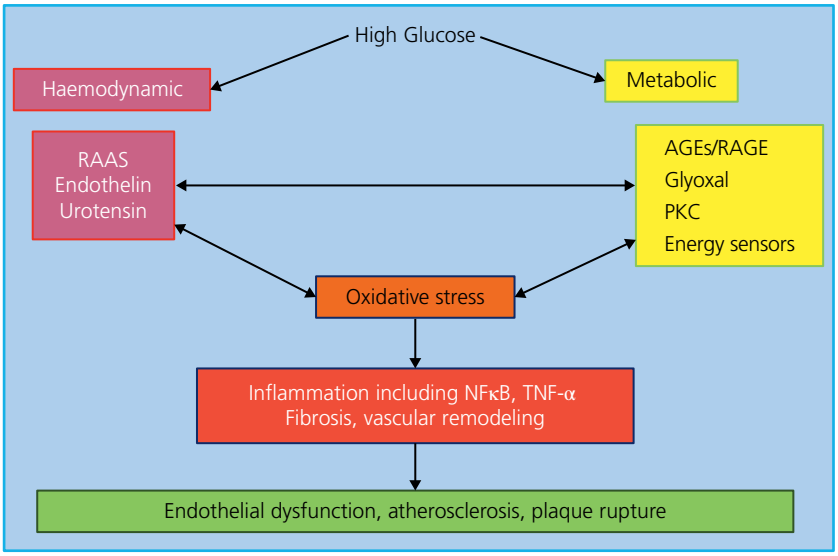

Figure 46.1 Haemodynamic and metabolic mediators contribute to the pathogenesis of diabetes vascular complications. Haemodynamic factors include the renin–angiotensin–aldosterone system (RAAS) and other vasoactive factors. Metabolic factors include glucose and glucose metabolites such as the formation of advanced glycation end-products (AGEs) including glyoxal, their interaction with the receptor RAGE, as well as energy sensors. Both pathways interact with each other and lead to oxidative stress and inflammation, thus promoting endothelial dysfunction and atherosclerosis. NFκB, nuclear transcription factor κB; PKC, protein kinase C; TNF-α, tumour necrosis factor α.

Pathogenesis of diabetic macrovascular disease

Chronic exposure of the vascular endothelium to hyperglycaemia induces an inflammatory response involving the adhesion and transmigration of monocytes through the vascular wall into the subendothelial space [15]. Furthermore, accelerated generation and vascular deposition of advanced glycation end-products (AGEs) in addition to interactions with the AGE receptor (RAGE) in diabetes initiate oxidative reactions that promote the oxidation of low-density lipoprotein (LDL) cholesterol (oxLDL) [16], which enhances the pro-inflammatory properties of the endothelium [17]. Monocytes differentiate into macrophages, which, via uptake of lipids, transform into foam cells and accumulate in the vascular wall. The early atherosclerotic process results in the formation of fatty streak lesions, which over time develop into more advanced lesions, characterized by infiltration with vascular smooth muscle cells (VSMCs), formation of a necrotic core, and further lipid accumulation [15]. In humans, these lesions can demonstrate features of instability and plaque rupture, including intraplaque haemorrhages in addition to heightened thrombogenicity.

Role of hyperglycaemia

A pivotal role for glycaemia and duration of diabetes exposure has been well established for microvascular complications in the UK Prospective Diabetes Study (UKPDS) study [18, 19]; however, the data was not as convincing for macrovascular disease. The importance of hyperglycaemia for macrovascular injury was subsequently extensively investigated in a series of studies. It was suggested that glycated haemoglobin (HbA_{1c}) acts as an independent and continuous risk factor for macrovascular disease [20–23]. For an increase in HbA_{1c} from 5.5% (37 mmol/mol) to 9.5% (80 mmol/mol), there is a 10-fold increase in microvascular disease endpoints, while the risk for macrovascular disease endpoints increases only twofold.

Clinical trials and hyperglycaemia

Clinical trials such as the Action to Control Cardiovascular Risk in Diabetes trial (ACCORD) [24], Action in Diabetes and Vascular disease: PreterAx and DiamicroN-MR Controlled Evaluation (ADVANCE) trial [25], and the Veterans Affairs Diabetes Trial (VADT) [26] explored the effect of tight glycaemic management on cardiovascular endpoints in people with type 2 diabetes. As observed in the initial reports of the Diabetes Control and Complications Trial (DCCT) in people with type 1 diabetes and in the UKPDS trial in people with type 2 diabetes, tight blood glucose management had little effect on macrovascular outcomes. This was further emphasized by subsequent studies including the ADVANCE [25] and ACCORD trials [24]. Both studies demonstrate no significant cardiovascular benefit, with the ACCORD study even suggesting possibly deleterious cardiovascular outcomes in association with tight glucose management.

One possible explanation for the lack of a positive effect of tight glycaemic management on cardiovascular outcomes may be the short duration of these trials (<5 years). Indeed, as best seen in the longer follow-up of the Steno-2 study [27] and a long-term follow-up of the UKPDS [28], the benefits of prior intensified cardiovascular risk management including aggressive glucose management may not appear for up to 10 years after initiation of the studies. Thus, in view of the relative lack of an impact on CVD with intensive glucose management, other risk factor modification strategies need to be emphasized. The recent publication of the ADVANCE-ON trial did not show a benefit of the initially intensive glucose-lowering treatment arm in terms of cardiovascular outcomes after six years of follow-up, whereas the initially treated blood pressure arm continued to show cardiovascular protection [29].

Consistent with these findings, a recent meta-analysis of the major cardiovascular trials including ACCORD, ADVANCE, and VADT demonstrated only a modest beneficial effect in CVD. In contrast, the evaluation of novel anti-diabetes drugs, such as sodium–glucose cotransporter-2 (SGLT-2) inhibitors [30] and glucagon-like peptide 1 (GLP-1) receptor agonists [31], has reported cardiovascular benefits with decreased cardiovascular and all-cause mortality in most trials, and this has had a significant impact on the understanding of glucose management and its association with cardiovascular outcomes.

The evidence for other anti-diabetes agents, such as dipeptidyl peptidase 4 (DPP-4) inhibitors, is less convincing and most trials have not demonstrated superior protection with respect to macrovascular disease [32, 33].

Direct and indirect glycotoxicity

Hyperglycaemia has direct and indirect toxic effects on vascular cells. Increased glucose levels enter the polyol pathway at an increased flux rate, leading to heightened formation of diacylglycerol. In addition, an increased flux of glucose into the hexosamine pathway may contribute to glucose-mediated vascular injury in diabetes. To investigate specifically hyperglycaemia-mediated atherosclerosis, aldose reductase transgenic mice have been studied [34]. These mice demonstrated increased glucose delivery via the polyol pathway and also showed early atherosclerosis, but did not develop advanced vascular lesions. It has been suggested that the formation of reactive dicarbonyls is a more reliable marker of glucose toxicity than the conventional measurements of fasting glucose or HbA_{1c} [35], although this is yet to be proven.

In Vitro studies

Cell culture experiments provide clear evidence that hyperglycaemia induces a range of pro-atherogenic effects [36]. Glucose directly activates monocytes–macrophages *in vitro*, initiating increased expression of cytokines such as interleukin 1β (IL-1β) and IL-6 [36]. Furthermore, this leads to protein kinase C (PKC) and nuclear factor κB (NFκB) activation, resulting in increased production of reactive oxygen species (ROS). Auto-oxidation of glucose can also lead to the formation of ROS and can mediate oxLDL. Scavenger receptors on activated macrophages can mediate the uptake of modified lipids such as the pro-atherogenic oxLDL. The formation of AGEs in the hyperglycaemic milieu can lead to the formation of modified albumin, which inhibits scavenger receptor class B type 1–mediated efflux of cholesterol to high-density lipoprotein (HDL). Therefore, prolonged hyperglycaemia can indirectly lead to a range of secondary changes, including increased ROS formation via activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, changes in lipid profile, cellular lipid accumulation, and foam cell formation, in addition to AGE-mediated modification of proteins leading to altered cellular structure and function.

Animal models

The study of atherosclerosis in diabetes has long been hampered by the lack of an appropriate animal model. Our group and others have developed a murine model of diabetes-associated macrovascular disease, the ApoE knockout (KO) mouse, rendered diabetic by multiple low doses of streptozotocin injections. This model is considered by the National Institutes of Health/Juvenile Diabetes Research Foundation (NIH/JDRF) co-sponsored Animal Models for Diabetes Complications Consortium (AMDCC) to be an appropriate model to study macrovascular disease in diabetes [37].

To address the separate roles of hyperglycaemia and dyslipidaemia in diabetes-associated atherosclerosis, mice deficient in the LDL receptor were bred with transgenic mice expressing a viral protein under control of the insulin promoter [38]. When infected with the virus, T cells mediate destruction of pancreatic β cells that express the viral protein, thus closely mimicking the autoimmune response in human type 1 diabetes. In these animals, atherosclerosis development was accelerated even on a normal diet, suggesting that hyperglycaemia was driving atherosclerosis in these mice [38, 39]. When the animals were placed on a high-fat diet, a further acceleration of atherosclerosis occurred, suggesting that glucose and lipids may act through synergistic mechanisms to accelerate atherosclerosis. Furthermore, plaque disruption and intraplaque haemorrhages, features of plaque instability and potential plaque rupture, were observed in this model [38].

There has been a lack of an appropriate animal model demonstrating features of plaque instability and rupture in diabetes. More recently Chen et al. have developed such a model using a tandem stenosis approach in the carotid artery. This model showed characteristic changes associated with plaque rupture, albeit not in the diabetic context [40].

Metabolic memory

The concept of *glycaemic memory* describes the deferred effects of prior glycaemic status on the subsequent development of diabetic complications. Chronic hyperglycaemia during the earlier stages of diabetes can precipitate or accelerate the development of complications later in the course of diabetes even when glycaemic levels are subsequently improved. Three studies have provided evidence for such a metabolic imprint, the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) trial in type 1 diabetes [2] and the Steno-2 trial [27] and UKPDS in type 2 diabetes [28]. These studies have shown that hyperglycaemia was associated with an increased subsequent burden of complications. Another study in people with type 2 diabetes, VADT, compared intensive with standard glucose management (HbA_{1c} 6.9% vs 8.4%, 52 mmol/mol vs 68 mmol/mol), but did not demonstrate significant cardiovascular protection after the participants had been exposed to hyperglycaemia for long periods (12–15 years) [26].

The concept of *metabolic memory* raises two important issues. First, hyperglycaemia may expose people with diabetes to its harmful effects years before type 2 diabetes is diagnosed. Indeed, 25% of people show complications at the time of diagnosis of type 2 diabetes. Therefore, it has been postulated that early diagnosis and strict glycaemic management may be pivotal to reduce the induction of this metabolic memory with subsequent development of long-term diabetes-related vascular complications. Second, glycaemic oscillations including peaks and troughs, which are not reflected in the HbA_{1c} levels [41, 42], may have a key role in mediating growth factor and cytokine expression in addition to inducing epigenetic changes [43]. Epigenetic mechanisms control the gene expression changes through enzyme-mediated epigenetic alterations, namely histone modification, DNA methylation, and non-protein coding RNAs, and are highly dynamic and respond to environmental stimuli such as hyperglycaemia.

There are many cellular and molecular processes that may contribute to the mechanisms underlying metabolic memory, with most of them relating to glycotoxicity. These pathways include the formation of AGEs, glycation of DNA, and increased flux of glucose metabolism, leading to increased oxidative damage, overproduction of PKC-β, and mitochondrial stress. Transient hyperglycaemia induces long-lasting activation of epigenetic changes in the promoter region of the NFκB subunit p65 in aortic endothelial cells both *in vitro* and *in vivo*. These hyperglycaemia-induced epigenetic changes were prevented by reducing mitochondrial superoxide production or superoxide-induced generation of α-oxoaldehydes such as methylglyoxal (Figure 46.2) [43]. These studies suggest that transient hyperglycaemia causes persistent atherogenic effects during subsequent normoglycaemia by inducing long-lasting changes in chromatin remodelling, and highlight a critical role for ROS in epigenetic modulation of glucose-responsive pathways. Specifically, hyperglycaemia results in recruitment of the mobilization of the histone methyl transferase Set7 to the nucleus, with increased H3K4 mono-methylation of the proximal promoter region of the

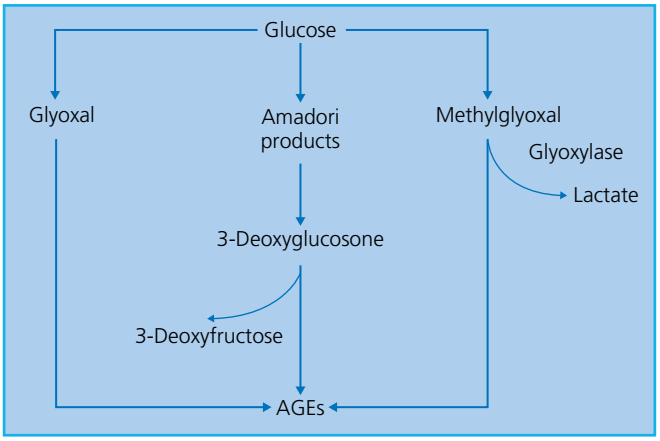

Figure 46.2 The formation of advanced glycation end-products (AGEs) can involve early glucose metabolites such as glyoxal and methylglyoxal, highly reactive dicarbonyls, and key precursors of AGEs.

NFκB subunit p65 gene. This process leads to increased expression of pro-atherogenic pathways including monocyte chemotactic protein 1 (MCP-1) and vascular cell adhesion molecule 1 (VCAM-1) [43]. Subsequent studies in mice that were initially diabetic but returned spontaneously to normoglycaemia have also demonstrated persistent upregulation of pro-inflammatory genes such as p65 and MCP-1 as a result of prior hyperglycaemia. Novel Set7 networks encompassing immune-inflammatory pathways [44], including antioxidant molecules such as heme oxygenase 1 by H3K4m1-dependent and H3K4m1-independent pathways, have been implicated in the development of macrovascular disease in diabetes [45]. Recent studies by Paneni et al. validated Set7 as an epigenetic regulator of vascular cell inflammation in people with diabetes, which was associated with an increase in the oxidative stress marker 8-isoPGF2α [46] and vascular dysfunction in individuals with diabetes. Furthermore, more detailed epigenetic studies revealed that changes in histone modifications as a result of prior hyperglycaemia also included changes in H3K9 methylation of the p65 promoter, in addition to effects on various histone methyl transferases and interestingly also demethylases such as LSD-1 [47]. In addition, H3K9 hyperacetylation of several genes including *HMOX1*, *HMOX1*, *IL-8*, *Cox2*, *TNF*α, and *MMP10* has been detected in vascular and immune cells in people with diabetes [48, 49].

An earlier study demonstrated that the gene repressive mark, H3K9me3, plays an important role in VSMC inflammation in diabetes. This study identified downregulation of the H3K9me3-writing enzyme, Suv39h1, and reduced levels of H3K9me3 on inflammatory genes responsible for VSMC-mediated inflammation in diabetic *db/db* mice [50]. Furthermore, dimethylation of H3K9 is associated with vascular complications of diabetes. In a rat model of diabetes, reduced levels of H3K9me2 correlated with the elevated expression of histone demethylase KDM3a in VSMCs [51].

BETs (bromodomain and extraterminal-containing protein family) specifically recognize acetylated lysine residues on histone tails and facilitate binding of transcription factors and the transcriptional machinery including RNA polymerase II [52]. The use of specific BET inhibitors like JQ-1 attenuates atherosclerosis and intimal hyperplasia in experimental models [52]. Importantly, the BET inhibitor apabetalone (RVX-208) prevents hyperglycaemia-induced upregulation of IL-1β, IL-6, and TNF-α in human endothelial cells and in aortic plaques in ApoE$^{-/-}$ mice [53]. Furthermore, analysis of non-randomized studies showed that treatment with apabetalone was associated with fewer cardiovascular events compared to placebo [54]. The recent phase III BETonMACE trial, designed to investigate the impact of apabetalone on cardiovascular outcomes in 2425 individuals with diabetes after an acute coronary syndrome, did not meet the primary cardiovascular endpoint of cardiovascular death, non-fatal myocardial infarction, or stroke [55]. However, the drug showed a highly favourable profile on secondary endpoints, namely heart failure.

Insulin resistance

Insulin resistance occurs in type 2 diabetes and in people with impaired glucose tolerance, and has been associated with increased cardiovascular risk [56–58]. There is now increasing evidence that insulin resistance promotes atherogenesis as an independent risk factor [59–61]. Furthermore, insulin resistance is often associated with a proatherogenic lipid profile that includes a high very low-density lipoprotein (VLDL) component, a low HDL, and small dense LDL.

In vitro studies have shown that insulin exerts both pro- and anti-atherogenic effects [62, 63], which has led to the hypothesis of pathway-specific insulin resistance (Figure 46.3). It has been suggested that insulin resistance towards glucose transport also affects resistance to the anti-proliferative effects of insulin, whereas the signalling pathways leading to cellular proliferation remain intact (Figure 46.3). Insulin signalling via phosphatidylinositol-3-kinase (PI3K) has been associated with antiproliferative and antithrombogenic effects, with decreased adhesion molecule expression such as MCP-1, VCAM-1, and intercellular adhesion molecule 1 (ICAM-1). Furthermore, nitric oxide (NO) production is mediated via the PI3K signal transduction pathway and therefore is impaired in insulin resistance. NO reduces oxLDL and proliferation of VSMCs. In contrast, effects on VSMC proliferation and migration are mediated via the Ras/Raf/MEKK/MAPK signal transduction pathway, which is further stimulated in the context of hyperinsulinaemia, suggesting that pathway-specific insulin resistance contributes to the proatherogenic effects of insulin. IL-6 decreases insulin-stimulated NO production from endothelial cells via decreased activity of insulin signalling mediated by enhanced TNF-α production [64]. Paradoxically, IL-6 increases insulin-stimulated glucose uptake into skeletal muscle and adipose tissue via enhanced insulin signalling, yet IL-6 and insulin have not been linked to increased TNF-α expression in skeletal muscle [64].

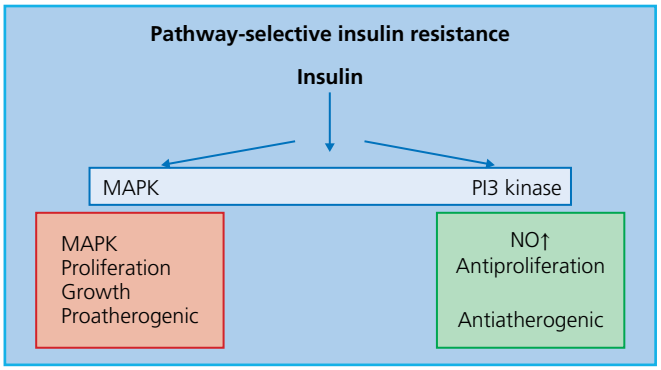

Figure 46.3 Pathway-selective insulin resistance leading to endothelial dysfunction and atherosclerosis. MAPK, mitogen-activated protein kinase; NO, nitric oxide; PI3 kinase, phosphatidylinositol 3 kinase.

Advanced glycation end-product formation

AGE formation originates from early glycation products, the Schiff bases, which form the more stable Amadori products such as 1-amino-1-deoxyfructose derivatives. The Amadori products undergo further enzymatic modifications resulting in several reactive intermediates such as 3-deoxyglucosone and methylglyoxal (Figure 46.2). Methylglyoxal reacts with amino, sulfhydryl, and guanidine functional groups in proteins, causing browning, denaturation, and redox-active diamine cross-linking between lysine residues of the target amino acids. Methylglyoxal also generates hydroimidazolones, N^{ε}-(carboxyethyl)lysine, a homologue of carboxymethyllysine (CML) and methylglyoxal–lysine dimer [65, 66]. The AGE-based cross-links are resistant to enzymatic degradation and therefore very stable [67]. The rate of AGE formation is dependent on multiple factors, including the ambient concentrations of various sugars including glucose, the extent of oxidative stress, and the duration of exposure to these various stimuli [68, 69].

More recently, research has been focused not only on AGE modifications on cellular and short-lived extracellular proteins, lipids, and DNA, but also on the impact of key intermediates including the highly reactive dicarbonylmethylglyoxal [35, 70]. Methylglyoxal is 20 000 times more reactive with proteins than glucose itself. Methylglyoxal formation may correlate better with glucose fluctuations observed in diabetes and may explain why post-prandial glucose concentrations are independent risk factors for CVD [71]. Impaired glucose metabolism and type 2 diabetes correlate with higher plasma methylglyoxal (MGO) levels. Furthermore, MGO-derived AGEs are associated with increased risk of cardiovascular events in people with type 2 diabetes [72]. In the experimental setting, oral administration of methylglyoxal to non-diabetic animals leads to accelerated atherosclerosis similar to that observed in diabetic animals in association with upregulation of vascular inflammatory markers [70].

The detoxifying enzyme glyoxalase-1 (GLO-1), which reduces methylglyoxal accumulation, may play a key role in diabetes-related vascular disease [72]. It is downregulated in diabetes and other states of inflammation, hypoxia, and ageing. Genomic studies have shown GLO-1 as a molecular mechanism in the development of CVD [73, 74].

Direct effects of vascular advanced glycation end-product accumulation

AGEs directly influence endothelial function [75] in addition to enhancing the evolution of macrovascular disease [76, 77]. AGEs mediate their effects both directly and via receptor-mediated mechanisms. AGE accumulation in the vascular wall is associated with changes in the structural integrity of proteins, disturbance of their cellular function, and degradation of these proteins [36]. AGEs accumulate on many proteins, including collagen, albumin, and apolipoproteins. Furthermore, the cross-linking of AGEs with matrix molecules can disrupt matrix–matrix and matrix–cell interactions. AGE cross-linking to collagens decreases vascular elasticity and reduces vascular compliance, resulting in increased vascular stiffness [78, 79]. In addition, AGEs can quench NO [75, 80] and generate ROS by stimulating NADPH oxidase activity [81].

Advanced glycation end-product–binding proteins

The receptor-mediated effects of AGEs occur via binding to proteins such as RAGE [82], AGE-R1 (p60), AGE-R2 (p90), and AGE-R3 (galectin-3), the ezrin–radixin–moesin (ERM) family of proteins [83], macrophage scavenger receptor ScR-11, and CD-36 [84]. The exact roles of AGE-R1, -R2, and -R3 have not been fully elucidated. Finally, the interaction between AGEs and several macrophage scavenger receptors, such as CD36 [84], has been postulated to promote atherosclerosis with studies using CD36 KO mice, supporting the view that CD36 promotes atherosclerosis [85].

Receptor for advanced glycation end-products

RAGE is a multiligand signal transduction receptor of the immunoglobulin superfamily of cell surface molecules that acts as a pattern recognition receptor [82]. In addition to binding ligands that actively participate in inflammation and immune responses, RAGE serves as an endothelial adhesion receptor for leucocyte integrins and promotes leucocyte recruitment and extravasation of infiltrating cells. Of direct relevance to diabetes-related macrovascular complications, RAGE is found on endothelial cells and monocytes–macrophages [77, 86, 87], and has been implicated in inflammatory lesions in many disorders [88].

Downstream effects of advanced glycation end-product receptor activation

Engagement of RAGE leads to activation of the proinflammatory transcription factor NFκB (Figure 46.4) [89]. AGE binding to RAGE activates various signalling pathways, including NADPH oxidase [81], MAPKs, $p21^{ras}$ [81], extracellular signal-regulated kinases (ERKs) [90, 91], and PKC, causing activation and translocation of NFκB [89]. Furthermore, expression of RAGE itself can be induced by NFκB [91]. RAGE expression within tissues is markedly enhanced in response to metabolic disturbances such as diabetes, dyslipidaemia, uraemia, and ageing, possibly because of accumulation of AGEs in these conditions [86, 88]. In plaques from diabetic ApoE KO mice, upregulation of connective tissue growth factor (CTGF) is AGE dependent [76] and may be mediated via RAGE. Intracellular accumulation of AGEs may also promote phenotypic conversion of VSMCs into foam cells within atherosclerotic plaques [92].

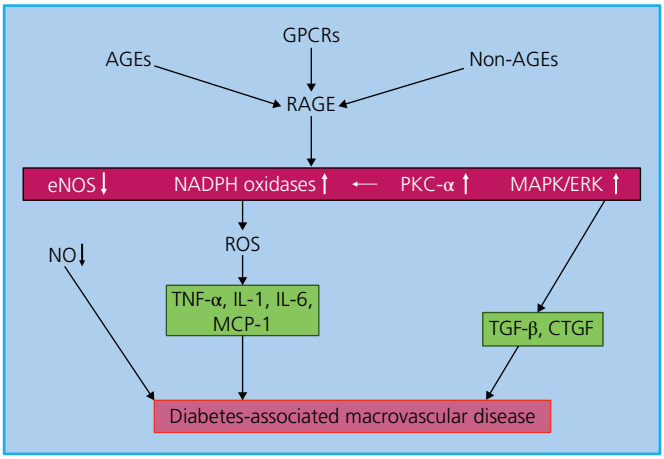

Figure 46.4 Activation of AGE receptor (RAGE) contributes to diabetes-associated macrovascular disease via increased production of reactive oxygen species (ROS), decrease in nitric oxide (NO) availability, and activation of the nuclear transcription factor κB (NFκB) and tumour necrosis factor α (TNF-α), in addition to activation of pro-fibrotic growth factors such as transforming growth factor β (TGF-β) and connective tissue growth factor (CTGF) associated with vascular remodelling. eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; GPCRs, G-protein–coupled receptors; MAPK, mitogen-activated protein kinase; MCP, monocyte chemotactic protein; NADPH, nicotinamide adenine dinucleotide phosphate; PKC, protein kinase C.

A link between the inflammatory signalling through the angiotensin II receptor type 1 (AT_1) and RAGE has recently been proposed. Indeed, the transactivation of RAGE mediates angiotensin II–induced inflammation and atherogenesis. When RAGE was deleted or inhibited, the adverse pro-inflammatory events triggered by the AT_1 receptor were prevented. Treatment with the mutant RAGE peptide S391A-RAGE362–404 inhibited transactivation of RAGE and attenuated Ang II–dependent inflammation and atherogenesis [93].

Transient intermittent hyperglycaemia accelerates atherosclerosis and increases myelopoiesis involving enhanced glucose uptake via GLUT1 as well as glycolysis in neutrophils. This event promotes the production of S100A8/A9 by neutrophils, which is also a RAGE ligand. The studies emphasize the importance of fluctuating glucose levels in the development of atherosclerosis that are not adequately captured by HbA_{1c} [94].

Studies reducing vascular advanced glycation end-product accumulation

Several pharmacological interventions have been used to reduce the accumulation of AGEs via decreasing the total AGE load or via chemical modification of existing AGEs into inactive forms [95, 96]. Aminoguanidine is a potent inhibitor of the formation of AGEs, scavenges reactive dicarbonyl AGE precursors [95, 96], and decreases oxidative damage to mitochondrial proteins [97]. In experimental and clinical diabetes, aminoguanidine treatment reduces microvascular [98] and more recently macrovascular complications in a model of accelerated atherosclerosis, the diabetic ApoE KO mouse [76].

Another potential agent that inhibits AGE accumulation is ALT-711 or alagebrium [99]. Based initially on a range of *in vitro* studies, this thiazolium compound and its original prototype, phenylthiazolium bromide [100], have been shown to cleave preformed AGEs, hence one of the postulated mechanisms of ALT-711 is as an AGE cross-link breaker [99].

The removal of established cross-links in rats with diabetes by ALT-711 is associated with reversal of the diabetes-induced increase in large artery stiffness, increased collagen solubility, and reduced vascular and cardiac AGE accumulation [79, 101–103]. In addition, alagebrium prevents the progression of nephropathy [104, 105], possibly via direct inhibition of PKC-α phosphorylation [106], thus reducing renal expression of vascular endothelial growth factor (VEGF). Treatment with ALT-711 in diabetic ApoE KO mice was associated with a significant reduction in atherosclerosis [76]. This anti-atherosclerotic effect was associated with reduced vascular AGE accumulation and RAGE expression. Alagebrium treatment was also associated with less inflammation and reduced expression of pro-fibrotic growth factors, in particular CTGF [107, 108]. In the clinical setting, ALT-711 reduces pulse pressure and improves vascular compliance in people with systolic hypertension [79].

Soluble advanced glycation end-product receptor

There are three major splice variants of RAGE [109]. First, the full-length RAGE receptor; second, the N-terminal variant that does not contain the AGE-binding domain; and third, a C-terminal splice variant, soluble RAGE (sRAGE), which does not contain the trans-membrane and effector domains. It remains controversial whether the effects of sRAGE are primarily as a decoy to ligands such as AGEs or whether sRAGE acts as a competitive antagonist to the full-length biologically active RAGE [109, 110].

Soluble advanced glycation end-product receptor and diabetes-associated atherosclerosis

sRAGE has been identified as having therapeutic value in a model of diabetes-associated atherosclerosis, the streptozotocin diabetic ApoE KO mouse [111, 112]. In the original study, Park et al. [112] reported that diabetic ApoE KO mice treated with sRAGE showed a dose-dependent suppression of atherosclerosis and reduced plaque complexity. These beneficial effects were independent of effects on glucose or lipid levels. Furthermore, AGE levels in these diabetic mice were suppressed in a dose-dependent manner by sRAGE to levels similar to those seen in non-diabetic mice. Furthermore, the effect of RAGE blockade with sRAGE was investigated in established atherosclerosis [111]. Administration of sRAGE decreased the expression of RAGE, in addition to reducing the number of infiltrating inflammatory cells and gene expression for transforming growth factor β (TGF-β), fibronectin, and type IV collagen in both the aorta and the kidney in association with a reduced plaque area. Therefore, it was concluded by these investigators that RAGE activation contributes not only to lesion formation, but also to the progression of atherosclerosis.

sRAGE treatment is also effective in reducing vascular complications in other models of atherosclerosis and diabetes. Atherosclerosis in the LDL receptor$^{-/-}$ mouse made diabetic by streptozotocin injection [113] was significantly attenuated by sRAGE treatment. ApoE KO mice bred onto a *db*/*db* background, a model of type 2 diabetes and deficient leptin receptor signalling, showed increased atherosclerosis that was significantly attenuated by daily sRAGE treatment [114].

To understand better the specific role of RAGE in the genesis of vascular lesions, mice selectively deficient in RAGE/ApoE ($RAGE^{-/-}$/$ApoE^{-/-}$) have been created [115]. These mice completely lack not only tissue-bound full-length RAGE, but also sRAGE. As had been predicted by the pharmacological intervention studies directed towards the RAGE ligands and AGEs, RAGE KO mice bred onto an $ApoE^{-/-}$ background showed a marked reduction in plaque area in the presence and absence of diabetes [105, 106]. RAGE deletion has been investigated in streptozotocin diabetic RAGE/ApoE KO mice and showed a significant reduction in atherosclerotic plaque area compared with diabetic ApoE KO mice expressing RAGE. These vascular changes seen in the streptozotocin diabetic double RAGE/ApoE KO mice were associated with reduced inflammation, less accumulation of RAGE ligands such as S100/CML, decreased infiltration by macrophages and T lymphocytes, and a reduction in expression of pro-fibrotic and pro-inflammatory growth factors and cytokines [115, 116].

These promising results with RAGE antagonism have encouraged the development of RAGE-neutralizing compounds for clinical use. The RAGE-modulating agent TTP488 is currently being considered in phase II clinical trials in people with Alzheimer disease, with some positive results [117]. Another compound, TTP4000, is currently in phase I clinical trials. The recent findings about the transactivation of RAGE with glucocorticoid (GRC) receptors may hold promise for novel approaches to block the pro-atherosclerotic action of RAGE [93].

Interaction with the renin–angiotensin–aldosterone system

Because diabetes-related complications appear to be multifactorial in origin and involve interactions between haemodynamic pathways such as the RAAS and metabolic pathways such as hyperglycaemia and the formation of AGEs, there has been

increasing investigation of the potential links between these various pathways (Figure 46.1) [118]. There is evidence that AGE accumulation can induce an upregulation of certain components of the RAAS, although these studies have been performed predominantly in the renal context [119]. Furthermore, angiotensin-converting enzyme (ACE) inhibition appears to confer its end-organ protective effect partly via a reduction in AGEs and an increase in sRAGE [120]. Therefore, the status of the RAAS could represent a key modulator in AGE-induced diseases. More recently, other therapeutic interventions shown to be anti-atherosclerotic have been reported to exert part of their vasculo-protective effect via inhibition of the AGE/RAGE pathway. These include angiotensin II receptor blockers (ARBs), peroxisome proliferator-activated receptor α (PPAR-α), and PPAR-γ agonists and statins [121–123].

It is now considered that the pro-inflammatory signalling of the AT_1 receptor is at least in part mediated by the transactivation of the cytosolic tail of RAGE, the receptor for AGEs, thus linking metabolic and haemodynamic pathways directly via two distinct receptors.

Role of vasoactive hormones in diabetes-related atherosclerosis

Classic renin–angiotensin–aldosterone system

Renin was described more than 100 years ago by Tigerstedt and Bergman [124]. Nevertheless, our understanding of the RAAS is still not complete and has grown increasingly complex over the last decade. The classic pathway is now very well characterized (Figure 46.5). The generation of angiotensin (AT) I and II is not restricted to the systemic circulation and also takes place in vascular and other tissues (Figure 46.5) [125].

Novel aspects of the renin–angiotensin–aldosterone system: ACE2

In 2000, a further enzyme associated with the generation of angiotensin peptides was identified; ACE2 is a carboxypeptidase with sequence similarity to ACE [126]. ACE2 does not generate angiotensin II but increases the formation of AT-(1–7) (Figure 46.6). This heptapeptide causes vasodilatation and has growth-inhibitory effects [127]. Further research, including into specific inhibitors, is needed to elucidate the many functions of ACE2 inside and outside the RAAS.

Angiotensin receptors

The effects of all angiotensin peptides are mediated through specific cell surface receptors (Figures 46.5 and 46.6). The AT_1 receptor mediates most of the effects usually associated with angiotensin II. The role of the AT_2 receptor subtype remains controversial, but it appears to antagonize certain effects of angiotensin II mediated via the AT_1 receptor [128]. Its role in the macrovasculature remains controversial [129].

Role of the renin–angiotensin–aldosterone system in macrovascular disease

Local RAAS activation has an important role in the pathogenesis of diabetes-induced endothelial dysfunction and atherosclerosis [130–132]. As a result, there is a strong rationale for blockade of the RAAS to prevent cardiovascular events in individuals with diabetes. In addition, several clinical trials [133–138] have suggested that blockade of the RAAS may protect against the development of type 2 diabetes.

Renin–angiotensin–aldosterone system and regenerative endothelial cell repair

The RAAS has a role in affecting the number of regenerative endothelial progenitor cells in individuals with diabetes. An increased concentration of circulating endothelial progenitor cells,

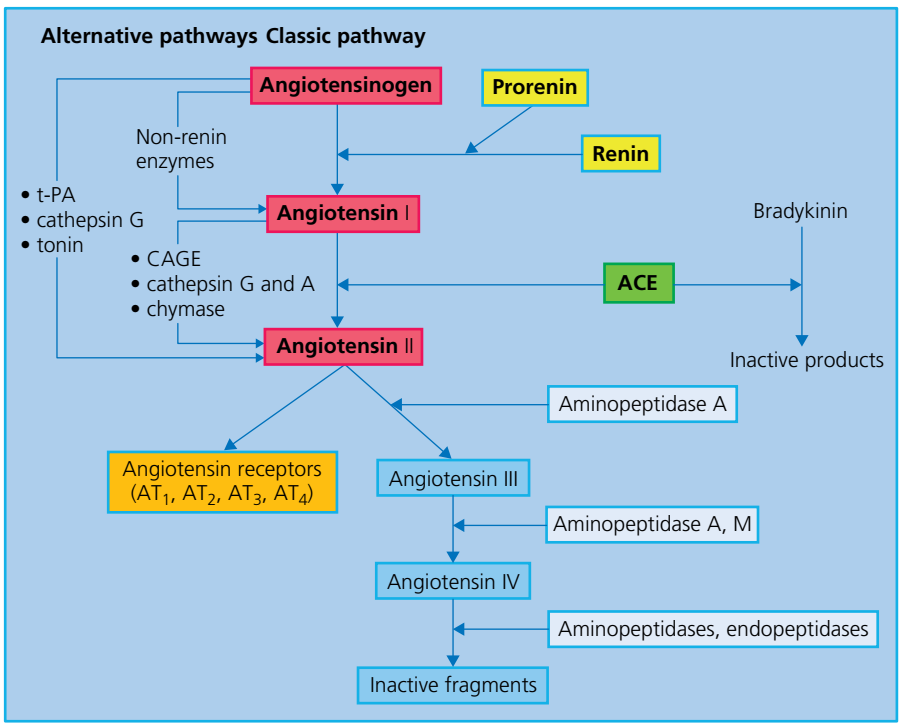

Figure 46.5 Overview of the enzymatic cascade of the renin–angiotensin–aldosterone system (RAAS): classic and alternative pathways. In the classic pathway, renin cleaves the decapeptide angiotensin I (AT I) from angiotensinogen. AT I is then converted to angiotensin II (AT II), which acts through several receptor subtypes, AT_1 and AT_2 receptors being the more relevant in the vasculature. CAGE, chymostatin-sensitive angiotensin II-generated enzyme; t-PA, tissue plasminogen activator.

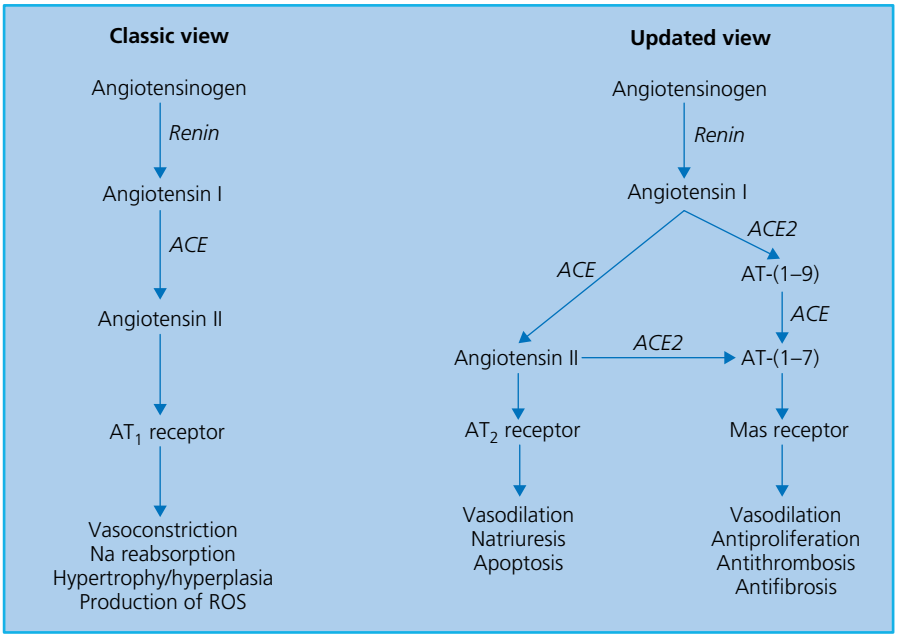

Figure 46.6 New aspects of the renin–angiotensin–aldosterone system (RAAS) components and its interactions. The classic RAAS illustrates the main pathway for angiotensin II (AT II) generation from angiotensin I (AT I) via ACE, with effects being mediated via the AT_1 receptor. The updated view illustrates the new components of the RAAS in which ACE2 has a role in degrading AT I to AT-(1–9) and AT II to the vasodilator AT-(1–7), which acts through the Mas receptor.

which are believed to maintain the integrity of the vascular endothelium, has been associated with a favourable cardiovascular outcome in people with coronary artery disease [139]. A study in individuals with type 2 diabetes [140] suggested that treatment with olmesartan, an ARB, increases the number of regenerative endothelial progenitor cells, which could contribute to the beneficial cardiovascular effects seen with AT_1 receptor blockade.

Role of AT-(1–7) and ACE2 in endothelial dysfunction

It has been hypothesized that disruption of the ACE–ACE2 balance may result in abnormal blood pressure, with increased ACE2 expression protecting against hypertension, and ACE2 deficiency causing hypertension (Figure 46.6) [139, 141]. AT II produces endothelial dysfunction through different pathways, such as increasing oxidative stress and exerting proliferative and prothrombotic activities [142], while AT-(1–7), which is generated by the enzyme ACE2, promotes the release of NO and prostaglandins [143, 144] and potentiates bradykinin effects in different experimental models [143, 145]. AT-(1–7) also inhibits growth of VSMCs [146], platelet aggregation and thrombosis [147], inflammation, fibrosis [148], and oxidative stress [149], which in turn might lead to restoration of endothelial function. It appears that AT-(1–7) can antagonize AT II effects, not only by the stimulation of other vasodilators but also through AT_1 receptor inhibition. In this regard, Kostenis et al. reported that the Mas receptor, which is increasingly considered to be the major receptor conferring the biological effects of AT-(1–7), seems to act as a physiological antagonist of the AT_1 receptor, thus counteracting many of the actions of AT II at the endothelial level [150].

Renin–angiotensin–aldosterone system activation and atherosclerosis

Clinical and experimental evidence clearly indicates that activation of the RAAS is central to almost all these pro-atherosclerotic pathways (Figure 46.7) [132, 151]. Diet et al. [131] observed increased ACE protein accumulation within the atherosclerotic plaque in human coronary arteries, suggesting that ACE may contribute to increased production of local AT II, which may participate in the pathophysiology of artery disease. There is also evidence that AT II and the AT_1 receptor are overexpressed in atherosclerotic plaques [130, 152–154]. Blockade of the RAAS with an ACE inhibitor or an AT_1 receptor antagonist prevents atherosclerosis by mechanisms involving inhibition of pro-inflammatory molecules such as VCAM-1 and MCP-1 and pro-sclerotic and pro-proliferative cytokines such as CTGF and platelet-derived growth factor [130, 154].

Production of pro-inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, have a major role in the pathogenesis of atherosclerosis [155]. IL-6, ACE, and AT_1 receptors have been detected in stable and unstable atherosclerotic plaques [153, 156]. AT II stimulates the redox-sensitive nuclear transcription factor, NFκB, which could serve as a unifying signalling system for inflammatory stimuli in atherogenesis through enhanced expression of adhesion molecules ICAM-1 and VCAM-1, E-selectin, MCP-1, and IL-8. Both ACE inhibitors and AT_1 receptor blockers decrease the expression of several adhesion molecules, thus confirming that the chronic inflammatory response associated with atherosclerosis appears to be modulated by AT II at every level and can be targeted therapeutically by RAAS inhibition [132, 157, 158].

The sustained pro-inflammatory state seems to play an important part in the transformation of a stable atherosclerotic plaque into a vulnerable plaque prone to rupture. Plaque rupture has been connected with activation of matrix metalloproteinases in the fibrous cap of the atherosclerotic lesion [159], and AT II is implicated in matrix metalloproteinase activation, both through direct action and through induction of pro-inflammatory cytokines such as IL-6.

ACE2 and diabetes-accelerated atherosclerosis

Although studies on the expression and activity of ACE2 in atherosclerosis are limited, there is increasing evidence that such more recently identified components of the RAAS may be involved in the development and progression of atherosclerosis. Zulli et al. [160]

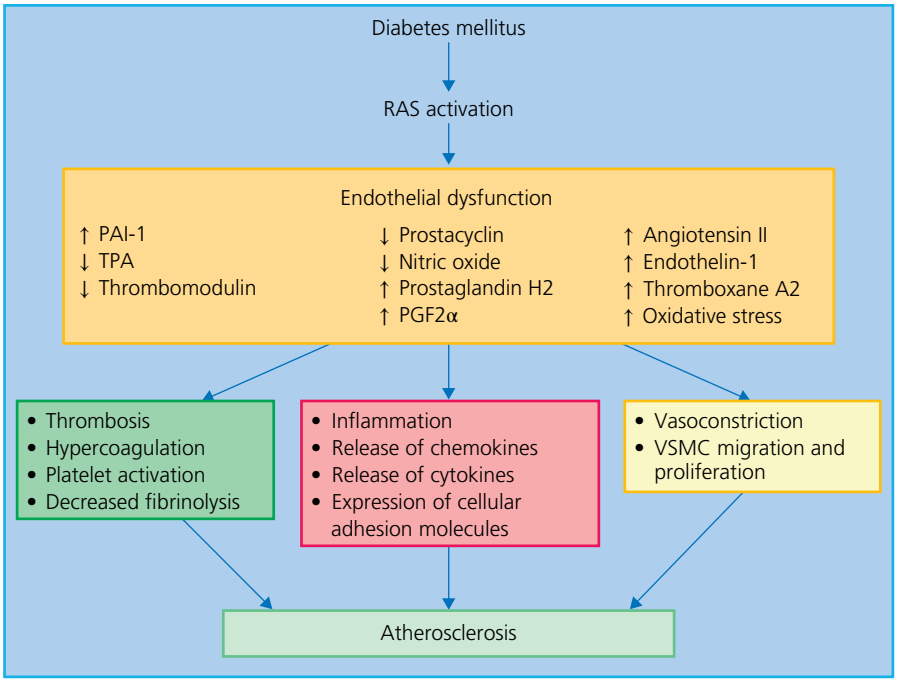

Figure 46.7 Effects of diabetes-induced renin–angiotensin–aldosterone system (RAAS) activation on mechanisms associated with endothelial dysfunction and atherosclerosis. In diabetes, activation of RAAS induces endothelial dysfunction that is characterized by vasoconstriction, inflammation, cellular growth, and thrombosis. By losing its protective properties, dysfunctional endothelium is a major promoter of atherogenesis and, consequently, cardiovascular events. PAI-1, plasminogen activator inhibitor-1; TPA, tissue plasminogen activator; VSMC, vascular smooth muscle cell.

have shown very high expression of ACE2 in endothelial cells, macrophages, and α-smooth muscle cells within atherosclerotic plaques in a rabbit model of atherosclerosis. It is unclear whether this increase in ACE2 is in response to injury in an attempt to protect the vessel by increasing levels of AT-(1–7).

In the human context, there is significant activation of the cardiac RAAS after coronary artery occlusion, and RAAS blockade reduces remodelling and improves survival in humans after myocardial infarction. Cardiac ACE2 expression and activity are also increased with experimental myocardial infarction [161]. Studies using ACE2 KO mice crossed with the atherosclerosis-prone ApoE$^{-/-}$ mouse have shown that ACE2 KO mice develop a similar degree of atherosclerosis to diabetic ApoE$^{-/-}$ mice, with a concomitant activation of inflammatory markers [162]. The induction of streptozotocin diabetes in ACE2/ApoE KO mice was not associated with a further increase in plaque area, suggesting that the downregulation of ACE2 in diabetes plays a key role in the development of atherosclerosis [163]. All these observations suggest that an imbalance in the RAAS plays a central role in the pathogenesis of atherosclerosis, and that the preservation and augmentation of ACE2 expression and activity represent a potential therapeutic target for the prevention of CVD in diabetes.

Renin–angiotensin–aldosterone system and oxidative stress

Local production of ROS has a pivotal role in atherosclerosis, specifically in the diabetic milieu. Increased vascular superoxide production is seen in aortas from diabetic atherosclerotic ApoE KO mice [121]. These changes were mediated by increased NAD(P)H oxidase (Nox) activity in the aorta with increased expression of various Nox subunits including p47phox, gp91phox, and rac-1 [121]. Increased local vascular ROS generation in diabetes is further supported by the demonstration of increased nitrotyrosine staining in these diabetic plaques [164–166]. Interventions that reduce vascular superoxide production such as PPAR-α and PPAR-γ agonists have been associated with reduced plaque formation, further emphasizing the link between vascular oxidative stress and atherosclerosis [121, 167]. Furthermore, the deletion of antioxidant enzymes such as glutathione peroxidase, specifically the Gpx1 isoform in the vascular wall, results in an increase in plaque area particularly in the diabetic context via increases in inflammatory mediators including adhesion molecules and chemokines [168]. Treatment of GPx1-deficient mice with the Gpx1 analogue, ebselen, reduced oxidative stress variables and atherosclerosis in diabetic GPx1/ApoE KO mice [169]. Furthermore, in the Gpx1/Apo E double KO mice, there was associated upregulation of RAGE, further linking vascular RAGE expression to increased oxidative stress and accelerated atherosclerosis in settings such as diabetes [168].

Therapeutic implications

Renin–angiotensin–aldosterone system inhibition and cardiovascular protection

Pharmacological therapy that interrupts the RAAS may afford special benefits in reducing CVD in people with diabetes [135, 170, 171]. In a *post hoc* subgroup analysis of the Captopril Prevention Project (CAPP) study, participants with diabetes treated with captopril fared significantly better than those treated with conventional therapy (β-blockers and diuretics) in terms of primary endpoint and also for myocardial infarction, all cardiac events, and total mortality [171]. These relative beneficial effects of ACE inhibitor therapy were particularly striking in those at highest risk, specifically those with the highest median fasting glucose or those with more elevated blood pressure. This is in contrast to the UKPDS [172], in which there were comparable cardiovascular benefits for people with type 2 diabetes who were randomized to captopril or atenolol, perhaps reflecting a lower CVD risk in the individuals with newly diagnosed diabetes in the UKPDS.

In MICRO-HOPE, a substudy of the Hypertensive Old People in Edinburgh (HOPE) study [173] that included 3577 individuals who had diabetes and one other CVD risk factor, there was a risk reduction of 25% for combined cardiovascular events, 37% for cardiovascular mortality, 22% for myocardial infarction, and 33% for stroke. In the Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET) study, the incidence of cardiovascular events was less in participants with type 2 diabetes and hypertension treated with fosinopril than the amlodipine-treated group [174]. The European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) [175] showed that ACE inhibition reduced cardiovascular mortality and morbidity in participants with established coronary artery disease without left ventricular dysfunction. The data from these trials were pooled with those of the Quinapril Ischemic Event Trial (QUIET) [176] study in a meta-analysis that included 31 555 participants [177]. This analysis showed that, compared with placebo, ACE inhibitor therapy produced a significant 14% reduction in all-cause mortality and myocardial infarction, a 23% reduction in stroke, and a 7% statistically significant reduction in revascularization procedures. The ADVANCE study [25, 178] showed that the administration of the ACE inhibitor perindopril and the diuretic indapamide in high-risk people with type 2 diabetes induced a reduction in macrovascular outcome compared with placebo.

Reports of trials with ARBs indicate that these agents have cardiovascular protection effects in individuals with type 2 diabetes similar to those observed with ACE inhibitors. In the Losartan Intervention for Endpoint reduction in hypertension (LIFE) study [135], treatment with losartan in people with type 2 diabetes and left ventricular hypertrophy resulted in a significant reduction in death from CVD and all-cause mortality. An analysis of the large Reduction of Endpoints in NIDDM with Angiotensin II Antagonist Losartan (RENAAL) study showed that treatment with losartan in participants with type 2 diabetes, nephropathy, and left ventricular hypertrophy reduced the cardiovascular risk to levels similar to those observed in individuals without left ventricular hypertrophy [179]. The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) [180] showed that the ARB telmisartan provides a benefit similar to that of a proven ACE inhibitor such as ramipril in high-risk people with CVD or those with diabetes and end-organ damage. This is a population similar to that examined previously in the HOPE study. Furthermore, in the ONTARGET study, the combination of ramipril with telmisartan, despite the further lowering of blood pressure, did not reduce the risk of cardiovascular events compared with an ACE inhibitor alone, but was associated with additional adverse effects including hypotension and renal dysfunction. Hence an ACE inhibitor, or possibly an ARB, is an initial antihypertensive agent of choice in people with diabetes because these agents have the capacity to prevent or delay the development of diabetic macrovascular complications, thus significantly reducing cardiovascular mortality and morbidity.

Endothelin system

Endothelin (ET) was first discovered in 1988 by Yanagisawa et al. [181] and is one of the most potent vasoconstrictors. There are three distinct ET genes that encode different mature endothelin sequences, designated ET-1, ET-2, and ET-3. Big ET-1 is converted into mature 21 amino acid ET-1 by ET-converting enzyme. ET-1 is predominantly present in endothelial cells. In 1990, the ET_A and ET_B receptor subtypes [182] were cloned. ET_A receptors are found in VSMCs and mediate vasoconstriction and cell proliferation (Figure 46.8). ET_B receptors are found in endothelial cells (ET_{B1}), where they mediate vasodilation via the release of NO, and on smooth muscle cells, where they may elicit vessel contraction and cell proliferation (Figure 46.8).

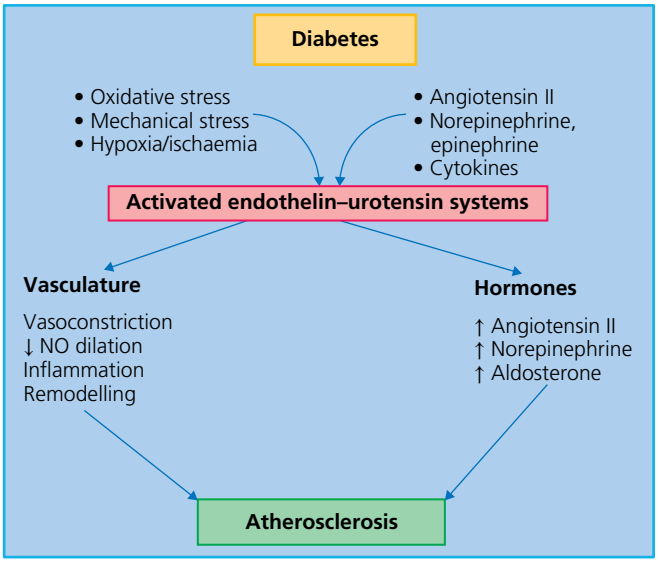

Figure 46.8 Proposed mechanisms of the endothelin and urotensin systems on atherosclerosis in diabetes. In diabetes, activation of the endothelin system induces vasoconstriction, vascular smooth muscle cell proliferation, wall thickening, inflammation, and tissue remodelling, thus leading to the development and progression of atherosclerosis.

Role of endothelin in diabetes-related macrovascular complications

Plasma concentrations of ET-1 are increased in people with type 2 diabetes complicated with atherosclerosis compared with those without diabetes with atherosclerosis and healthy individuals [183]. Kalogeropoulou et al. [184] demonstrated increased ET-1 levels in people with diabetes and carotid atherosclerosis. ET stimulates the production and release of inflammatory cytokines from monocytes [185] and enhances the uptake of LDL cholesterol by these cells, promoting a phenotypic change into foam cells [186]. Cytokines released from monocytes–macrophages, in turn, stimulate ET-1 production, providing positive feedback for further cytokine production [187].

In several animal models, both ET_A receptor-selective and non-selective ET_A/ET_B receptor blockade inhibits the development of atherosclerotic lesions, suggesting that elevated vascular ET-1 tissue levels promote endothelial dysfunction and vascular structural alterations via the activation of ET_A receptors [186, 188]. Treatment with an ET_A receptor antagonist decreased the atherosclerotic lesion area in the aorta in ApoE knock-out mice [9, 189]. Similar results have been reported with a non-selective ET_A/ET_B receptor blocker in rabbits. The role of the ET_B receptor in atherosclerosis remains controversial at this stage, although it has been shown to have anti-atherosclerotic effects via stimulation of NO production [190].

Finally, some of the beneficial effects of ACE inhibitors in term of cardiovascular protection may be mediated at least in part by endothelin inhibition. Captopril inhibits endothelin release from

cultured human endothelial cells and decreases 24-hour urinary ET-1 excretion [191]. Furthermore, ET_A receptor antagonism appears to be beneficial in the treatment of diabetic nephropathy, but there are currently no data to support a protective effect on macrovascular disease in people with diabetes. More recently, endothelin receptor antagonists have been trialled in type 2 diabetes–related nephropathy. A study using avosentan had to be terminated prematurely owing to off-target effects leading to fluid retention, heart failure, and cardiovascular mortality [192]. It is possible that the antidiuretic effect mediated by activation of the ET_B receptor is responsible for this effect. Newer and more ET_A receptor-selective endothelin blockers, such as atrasentan, have been evaluated and have demonstrated a reduction in residual albuminuria in people with type 2 diabetes [193]. If these renoprotective effects will also translate into cardiovascular protection, as suggested in pre-clinical studies, they will need to be evaluated in long-term studies with predefined cardiovascular endpoints.

A recent study using endothelium-specific expression of ET-1 in diabetic $ApoE^{-/-}$ mice suggested that the pro-atherosclerotic effect of endothelin involves the pro-oxidant NADPH-oxidase Nox1 [194]. These studies are consistent with previous studies suggesting that Nox1 plays a pivotal role in diabetes-associated atherosclerosis [166] and that novel Nox inhibitors as well as ET blockers could provide vasculoprotection in diabetes [195].

Urotensin II

Several reports have revealed the powerful vasocontractile effect of urotensin II (UT II) consistent with a potential importance of this peptide in cardiovascular physiology and diseases (Figure 46.8) [196]. A specific UT II receptor was identified in 1999 [197]. Elevated circulating concentrations of UT II have been detected in people with various cardiovascular states including heart failure, hypertension [198], carotid atherosclerosis, pre-eclampsia and eclampsia, renal dysfunction, and diabetes mellitus [199]. In addition, upregulation of the urotensin receptor system has been found in individuals with congestive heart failure and pulmonary hypertension [200].

Role of urotensin II in atherosclerosis

Expression of UT II is upregulated in endothelial, myointimal, and medial smooth muscle cells of atherosclerotic human coronary arteries. Bousette et al. [10] demonstrated that UT II expression is increased in both atherosclerotic carotid arteries and aortas. Plasma UT II level is correlated positively with carotid atherosclerosis in people with essential hypertension [201]. In ApoE KO mice, urotensin expression was significantly higher than in wild-type control mice [202]. Chronic infusion of UT II enhances atherosclerotic lesions in the aorta of ApoE knockout mice by increasing ROS production and acyl-CoA–cholesterol acyl transferase 1 expression. UT II expression in endothelial cells and VSMCs is increased following balloon injury in rat carotid arteries [203]. Furthermore, treatment with a UT II receptor blocker was associated with a 60% reduction in intimal lesion development.

UT II is linked to the activation of the redox-sensitive enzyme NADPH oxidase in the vascular wall and increased expression of inflammatory cytokines (Figure 46.8). In human peripheral blood mononuclear cells, inflammatory stimuli including IL-1β and TNF-α strongly enhance urotensin receptor mRNA and protein expression [204]. Of direct relevance to atherosclerosis, UT II has been shown, predominantly in *in vitro* studies, to enhance LDL cholesterol and ROS production via NADPH oxidase and to promote monocyte recruitment.

Oxidative stress

Excessive production of ROS, in conjunction with dysfunctional antioxidant defence systems, shifts the redox state of the cellular environment in favour of oxidant species, a state termed *oxidative stress*. Clinically, people with diabetes exhibit increased expression of various markers of oxidative stress [205, 206] and reduced antioxidant capacity [207, 208]. Despite a strong theoretical basis, clinical trials of antioxidant treatments for the lowering of CVD burden have produced disappointing results [137, 209].

Role of reactive oxygen species in diabetes-accelerated atherosclerosis

Reactive ROS and its products can directly damage vascular endothelial cells leading to apoptosis [210], autophagy [211], and DNA damage [212, 213]. Aberrant activation of redox-sensitive signalling molecules including protein kinases and transcription factors also plays a central part in diabetes-mediated vascular pathology [214]. Increased ROS production is associated with the induction of inflammatory gene expression, which occurs via upregulation of redox-sensitive inflammatory gene master regulator NFκB [215].

Nicotinamide adenine dinucleotide phosphate oxidase production of reactive oxygen species

Several enzymatic and non-enzymatic sources contribute to pathological increases in ROS generation in the diseased vasculature, including Nox, nitric oxide synthetase (NOS), myeloperoxidase (MPO), and xanthine oxidase (XO) [216]. However, the Nox enzymes are widely recognized as the major ROS producers in the vasculature [217] and also represent viable pharmacological targets for the treatment of diabetes-associated vascular disease [218].

The Nox isoforms Nox1, Nox2, Nox4, and Nox5 are differentially expressed in vascular cells, and play unique roles in physiology and disease [217, 219]. Several groups, including our own, have demonstrated increased gene and protein expression of Nox1 and Nox4 in hyperglycaemic conditions associated with increased atherosclerosis [164–166, 220–223]. Important roles for Nox1-derived superoxide have been described for AGE-mediated VSMC activation [224] and diabetes-associated endothelial dysfunction [225]. Recent evidence has identified a central role for Nox1 in accelerating atherosclerosis in the aorta of diabetic mice [166]. Controversy surrounds the role of Nox4 in vascular disease. Nox4 is constitutively expressed and produces predominantly hydrogen peroxide [165, 217, 226]. Its role in vascular disease appears to be dependent on the disease and experimental model under investigation. More recently, a vasculoprotective role for Nox4 has been demonstrated in a model of long-term diabetes-associated atherosclerosis [165]. Studies focusing on endothelial cell function following ischaemia and AT II stimulation have shown protective effects of Nox4 [227–229]. In contrast, Nox4-derived ROS promotes cardiac hypertrophy [230] and cardiovascular ageing [231].

Nox5 is a calcium-dependent Nox isoform expressed in human endothelial and vascular smooth muscle cells [232] and also monocytes and macrophages [233]. The exact function of vascular Nox5 is not known, but it affects endothelial nitric oxide synthase (eNOS) [234] and VSMC proliferation [235]. In macrophages, Nox5 expression and activity were induced by treatment with the

pro-inflammatory cytokine interferon-γ (IFN-γ) [233], suggesting a link between Nox5 and inflammation [236]. However, the lack of Nox5 in mice and rats has hindered investigations, and this has resulted in the generation of humanized Nox5 transgenic mouse models of vascular disease [236, 237]. Nox5 is involved in uncoupling of endothelial NO synthase and is associated with age-related hypertension [238]. Furthermore, Nox5 was associated with a phenotypic switch of VSMCs and promoted extracellular vesicle–mediated vascular calcification [239].

Inflammation and immune responses

There is an altered immune response in diabetes-associated macrovascular disease [115, 223, 240]. In diabetes, elevated ROS upregulates the expression of pro-inflammatory genes that lead to foam cell formation [241]. Emerging links between Nox-derived ROS and innate-adaptive immune cell responses have provided insight into the potential immunomodulatory role of Nox in diabetes-associated atherosclerosis. Induction of Nox4 in human monocytes and macrophages is required for oxLDL-stimulated ROS production and cytotoxicity [242]. Gray et al. also identified an important role for Nox1-derived ROS in monocyte adhesion and macrophage accumulation in the lesions of diabetic ApoE$^{-/-}$ mice [166]. More recently, we described an immunomodulatory role of Nox1- and Nox4-derived ROS in diabetes-associated atherosclerosis in the aortic sinus of ApoE$^{-/-}$ mice [164]. In humans, T cells isolated from atherosclerotic plaques recognize and respond to oxLDL [243, 244].

Activation of the inflammasome in diabetes accelerates atherosclerosis development. Indeed, the recent Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) trial has provided proof of concept that canakinumab, an IL-1Ra inhibitor, reduced cardiovascular events in individuals with myocardial infarction [244]. This study included a high proportion of individuals with diabetes. Furthermore, NLRP3-inflammasome inhibitors such as MCC950 have shown attenuation of plaque formation and inflammation in the experimental setting [245].

Tumour necrosis factor–related apoptosis-inducing ligand and osteoprotegerin

TRAIL is a member of the TNF ligand family [246] and is expressed across all cell types of the vasculature, including macrophages of atherosclerotic plaques [247]. Both the membrane-bound and soluble forms of TRAIL rapidly induce apoptosis in multiple transformed cell lines and tumour cells, but not in normal cells [246, 248].

Osteoprotegerin is a member of the TNF receptor superfamily [249] that is produced by various tissues, including the cardiovascular system. Osteoprotegerin has two known TNF family ligands: receptor activator of NFκB ligand (RANKL) [250] and TRAIL [251]. Increasing experimental evidence suggests that both TRAIL and osteoprotegerin are involved in vascular pathophysiology.

The potential role of soluble recombinant (sr)TRAIL in the pathogenesis and/or treatment of diabetes-induced atherosclerosis has been investigated *in vivo* in streptozotocin diabetic ApoE$^{-/-}$ mice [252]. Repeated intraperitoneal injections of srTRAIL significantly attenuated plaque development and contributed to the stabilization of atherosclerotic lesions by selectively decreasing the number of infiltrating macrophages and increasing the VSMCs within the atherosclerotic plaques [252]. Diabetic rats treated with srTRAIL also had improved endothelial function and suppressed ROS generation [253]. Knockdown of Nox4 in VSMCs significantly reduced TRAIL-induced activity of the NFκB reporter gene and ICAM expression [254]. The potential clinical relevance of these results was corroborated by animal-based studies, which identified that TRAIL can be regulated by insulin levels and may be involved in regulating vascular tone [255], and two studies showing significantly lower srTRAIL serum levels in people with acute coronary syndrome compared with those with stable angina or normal coronary arteries [256, 257]. Furthermore, individuals with untreated diabetes had lower concentrations of circulating TRAIL than healthy people in association with reduced flow-mediated endothelium-dependent arterial dilatation. Diabetes treatment resulted in an increase in TRAIL concentrations and an improvement in flow-mediated endothelium-dependent arterial dilatation, but concentrations were still lower than in those without diabetes [253].

Osteoprotegerin-deficient mice demonstrated calcifications of the aorta and renal arteries [258], suggesting that osteoprotegerin might have a role in protecting against vascular calcification. Interestingly, a study in older women found a significant correlation between elevated osteoprotegerin serum levels and cardiovascular mortality [259]. The potential links between osteoprotegerin and vascular disease in humans have been further supported by the detection of a single-nucleotide polymorphism in the promoter region of the human gene for osteoprotegerin related to vascular morphology and function [256]. Several independent studies have reported elevated serum and/or plasma osteoprotegerin levels in people with diabetes, and in particular in people with diabetes and vascular complications [260–263]. Although some authors have proposed that the increase in osteoprotegerin levels may represent a defence mechanism against other factors that promote vascular pathologies, other studies support a pro-atherosclerotic role for osteoprotegerin in the vasculature [223, 264, 265].

Complement activation

The complement cascade is an important part of the body's innate immune system, activated via one of three pathways; the classical pathway, the lectin pathway, and the alternative pathway, which converge into a common terminal pathway (Figure 46.9). In addition, homeostasis is another important function of the complement system based on its ability to distinguish between healthy host cells and host cells presenting with damage-associated molecular patterns, for instance necrotic or apoptotic [266]. It is therefore intriguing that the complement system is being linked with diabetes complications and in particular the lectin pathway of complement activation, which is activated by pattern-recognition molecules recognizing specific molecular patterns of carbohydrates and acetylated moieties [267].

It is hypothesized that diabetes causes complement autoreactivity as a result of hyperglycaemia-induced alterations in the carbohydrate patterns decorating host cells, as well as by glycation-induced dysfunction of complement regulatory proteins that normally protect healthy host cells from complement attack, such as CD59 [268, 269]. Mannan-binding lectin (MBL) is the best studied pattern-recognition molecule of the lectin pathway and accumulates in various organs of diabetic animals, including the heart and the kidneys [270–272]. In a 12-year observational study, individuals with type 1 diabetes and high circulating MBL levels at baseline had an increased risk of dying during follow-up compared with those with lower MBL levels [273]. This indicates a genetic predisposition depending on the *MBL2* genotype as the circulating MBL

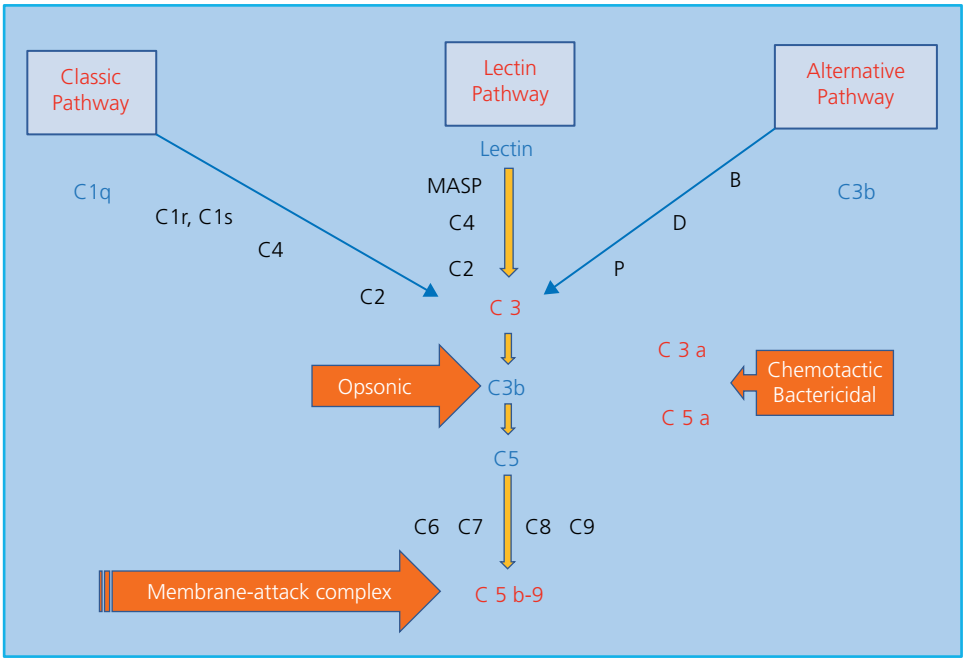

Figure 46.9 Schematic representation of the complement system. The complement cascade is activated by one of the three pathways: classic, lectin, or alternative. Activation leads to formation of the membrane-attack complex and also formation of opsonic, chemotactic, and bactericidal factors.

concentration varies many-fold between people as a result of polymorphisms of the *MBL2* gene and its promotor, whereas the within-person variation is much smaller [274, 275]. Accordingly, people with *MBL2* genotypes expressing high circulating MBL levels had an increased risk of dying during follow-up compared to those with *MBL2* genotypes expressing lower MBL levels, which indicates a causal role of MBL in the risk of mortality in type 1 diabetes [273]. Likewise, among individuals with type 2 diabetes followed for 15 years, those with high baseline MBL concentrations had a greater risk of dying than individuals with lower MBL levels [276]. However, in a recent study of more than 7000 individuals with type 2 diabetes followed for five years, a more detailed analysis was possible [277]. In this study, a U-shaped association between MBL and cardiovascular events was found, as both the lowest as well as the higher MBL levels were associated with an increased risk compared with the intermediate MBL concentrations [277]. In addition to these reports, numerous studies point to a critical role of MBL in diabetic kidney disease. In brief, high MBL levels represent an increased risk of kidney disease in both type 1 diabetes [278–281] and type 2 diabetes [282]. These observational data are supported by evidence of a causal role of MBL in the development of diabetic kidney disease in animal studies [270–272, 283]. Similarly, inhibition of complement factor C5 results in the attenuation of renal injury in diabetic rats [284]. In addition, clinical studies, aiming to inhibit further downstream in the complement cascade using the C5 inhibitor pexelizumab, initially showed reductions in mortality following acute myocardial infarction, as well as in mortality or myocardial infarction after coronary artery bypass graft surgery [285]. However, these beneficial clinical effects were not confirmed in a later and larger study [286].

The mechanisms linking the complement system with diabetes complications remain to be elucidated. However, an interesting concept is based on the membrane-attack complex, which is formed by the common terminal complement pathway. These complexes form pores penetrating target membranes and normally cause osmotic lysis of invading pathogens. However, sublytic membrane-attack complexes can form on mammalian cells, causing them to release growth factors, MCP-1, and IL-1 and to mediate inflammation, which is known to contribute to the development of diabetes complications [287]. Furthermore, complement activation causes NLPR3 inflammasome activation, which likewise induces inflammation via IL-1β and IL-18 [288, 289]. C5a receptor blockade attenuates inflammation and renal injury in a model of diabetes [290]. However, further studies are needed to determine if manipulation of the complement system represents a promising target in the treatment and prevention of diabetes-associated macrovascular disease.

Interventions to reduce diabetes-associated macrovascular complications

A range of interventions have been proposed for reducing the macrovascular complications of diabetes, including lifestyle modification, weight reduction, dietary changes, and regular exercise.

Glucose management

Optimal glucose management is pivotal for the prevention and treatment of microvascular complications of diabetes; however, based on clinical trials [19, 25, 28], the evidence for beneficial effects on macrovascular outcomes is less clear. Nevertheless, it has been suggested to aim for HbA_{1c} <7% (53 mmol/mol), but to be more cautious in those with underlying and pre-existing CVD. Since 2008, cardiovascular outcome trials have been required by regulators for licensing new glucose-lowering agents. These trials have shown that GLP-1 receptor agonists and SGLT-2 inhibitors reduce the risk of cardiovascular death, myocardial infarction, and stroke [291]. For example, in the Empagliflozin Cardiovascular Outcome Event Trial (EMPA-REG) study, the SGLT-2 inhibitor empagliflozin reduced cardiovascular and total mortality [292], with an associated benefit on renal endpoints including end-stage renal failure, doubling of serum creatinine, and albuminuria [293].

Table 46.1 Comparison of glucagon-like peptide 1 (GLP-1) receptor agonists and sodium–glucose cotransporter 2 (SGLT-2) inhibitors and their effect on cardiovascular events and cardiovascular death.

Drug type	Study name	Drug name	MACE Hazards ratio (95% CI)	Cardiovascular death – Hazard ratio (95% CI)
GLP-1 receptor agonist	ELIXA	Lixisenatide	1.02 (0.89 to 1.17)	0.89 (0.78 to 1.22)
	LEADER	Liraglutide	0.87 (0.78 to 0.97)	0.78 (0.66 to 0.93)
	SUSTAIN-6	Semaglutide	0.74 (0.58 to 0.95)	0.98 (0.65 to 1.48)
	EXSCEL	Exenatide once weekly	0.91 (0.83 to 1.00)	0.88 (0.76 to 1.02)
	Harmony	Albiglutide	0.78 (0.68 to 0.90)	0.93 (0.73 to 1.19)
	REWIND	Dulaglutide	0.88 (0.79 to 0.99)	0.91 (0.78 to 1.06)
	PIONEER 6	Oral semaglutide	0.79 (0.57 to 1.11)	0.49 (0.27 to 0.92)
SGLT-2 inhibitor	EMPA-REG	Empagliflozin	0.86 (0.74 to 0.99)	0.62 (0.49 to 0.77)
	CANVAS	Canagliflozin	0.86 (0.75 to 0.97)	0.87 (0.72 to 1.06)
	DECLARE-TIMI	Dapagliflozin	0.93 (0.84 to 1.03)	0.98 (0.82 to 1.17)
	CREDENCE	Canagliflozin	0.83 (0.68 to 1.02)	0.78 (0.61 to 1.0)
	Vertis CV	Ertugliflozin	0.97 (0.85 to 1.11)	0.92 (0.77 to 1.11)

CI, confidence interval; MACE, major adverse cardiovascular events.

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study, which evaluated the effects of the GLP-1 receptor agonist liraglutide, also showed clear benefits on cardiovascular and renal disease [294]. These positive findings emphasize the importance of these novel drugs on cardiovascular outcomes in people with type 2 diabetes. However, despite the clear evidence of reduction in overall and cardiovascular mortality, renoprotection, and reduction in heart failure, the evidence for a direct atheroprotective effect with these new agents is less clear.

A recent meta-analysis evaluating the effect of SGLT-2 inhibitors on macrovascular complications has shown that these drugs significantly reduced the risk of major adverse cardiovascular events (MACE) as well as cardiovascular death, compared to placebo [30, 291] (Table 46.1). Specifically, the SGLT-2 inhibitor empagliflozin showed the largest reduction in MACE [292] and was the only SGLT-2 inhibitor that showed a reduction in the risk of cardiovascular death. Canagliflozin [295, 296] and empagliflozin [292] also demonstrated a reduction in MACE, while dapagliflozin [297] and ertugliflozin [298] did not demonstrate such an effect.

GLP-1 receptor agonists have also been assessed for their role in reducing macrovascular complications in diabetes in several clinical trials [31] (Table 46.1). A recent meta-analysis demonstrated a significant reduction in MACE by 12%, cardiovascular death by 11%, stroke by 11%, myocardial infarction by 9%, all-cause death by 12%, heart failure by 9%, and kidney disease by 12%, without significant heterogeneity across the studies, suggesting a class effect for cardiovascular and renal outcomes [31].

Liraglutide (LEADER [294]), semaglutide (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes, SUSTAIN-6 [299]), albiglutide (Harmony Outcomes [300]), and dulaglutide (Researching Cardiovascular Events with a Weekly Incretin in Diabetes, REWIND [301]) significantly reduced the risk for the primary composite cardiovascular endpoint, which included death from cardiovascular cause, non-fatal myocardial infarction, and non-fatal stroke. In comparison, lixisenatide (Evaluation of Lixisenatide in Acute Coronary Syndrome, ELIXA [302]), exenatide once weekly (Exenatide Study of Cardiovascular Event Lowering, EXSCEL [303]), and oral semaglutide (Peptide Innovation for Early Diabetes Treatment, PIONEER 6 [304]) were not found to reduce cardiovascular events. Furthermore, liraglutide significantly reduced the risk of death from cardiovascular causes and semaglutide (non-oral) reduced the risk of non-fatal stroke compared to placebo.

The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) [305] and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and Reduced Ejection Fraction (EMPEROR-Reduced) [306] trials have shown the efficacy and safety of SGLT-2 inhibitors in improving cardiovascular mortality and morbidity in individuals with heart failure and reduced ejection fraction (HFrEF) with and without diabetes. These drugs have become a key part of heart failure therapy and are effective in reducing cardiovascular death or hospitalization for heart failure, regardless of the presence or absence of diabetes.

While these studies indicate that both SGLT-2 inhibitors and GLP-1 receptor agonists may reduce the risk of macrovascular complications in diabetes in high-risk individuals, it appears that some agents are better than others. It remains unclear whether the vasculoprotective effects of these drugs are also seen in individuals with early atherosclerotic disease or in terms of primary prevention. Furthermore, the glucose-independent mechanisms of these cardiovascular benefits of SGLT-2 inhibitors or GLP-1 receptor agonists have not been clearly delineated as yet. Current clinical trials will evaluate the effects of dual SGLT-2 inhibition and GLP-1 receptor agonism to assess potential synergistic or additive macrovascular protection in diabetes and in CVD without diabetes [30, 31].

These medications have now been implemented into guidelines [307], suggesting GLP-1 receptor agonists or SGLT-2 inhibitors as the preferred therapy after metformin in people with type 2 diabetes and established CVD.

Hypertension

Epidemiological studies have shown that the risk of cardiovascular events and mortality starts at blood pressure values as low as 115/75 mmHg for the general population and doubles for every increase of 20 mmHg in systolic and 10 mmHg in diastolic blood pressure (Chapter 47). The question of what systolic or diastolic blood pressure level should be targeted has not been completely

answered by currently available outcome trials. Based on studies such as the Hypertension Optimal Treatment (HOT) study [308], UKPDS [172], and the Appropriate Blood Pressure Control in type 2 Diabetes (ABCD) trial [309], a maximum systolic BP of 130–135 mmHg should be the goal for people with diabetes.

The ADVANCE trial [25] evaluated the effect of a fixed dose of perindopril and indapamide on macrovascular and microvascular outcomes in participants with type 2 diabetes. The treatment group showed a mean reduction in systolic and diastolic blood pressure of 5.6 and 2.2 mmHg, respectively, which was associated with an 18% reduction in cardiovascular deaths and a 14% reduction in coronary events in comparison with the control group. No lower limit for blood pressure reduction appears to exist at which benefits related to cardiovascular outcomes are not observed, with a similar pattern reported subsequently for renal disease [310]. The later ACCORD trial tested the effects of lowering blood pressure below 140/90 mmHg on cardiovascular outcomes [178]. Specifically, it aimed to evaluate if a blood pressure reduction to 120 mmHg systolic would further reduce the cardiovascular event rate. In the ADVANCE-ON trial, after six years of follow-up, benefits on cardiovascular outcomes were still present among those originally assigned to blood pressure–lowering therapy, but there was no evidence that glucose lowering had long-term benefits with respect to mortality or macrovascular events [29].

Choice of antihypertensive treatment

Experimental studies have clearly demonstrated a reduction in atherosclerosis with RAAS inhibitors, with a possible superiority of ACE inhibitors compared with ARBs in type 2 diabetes; however, there are no conclusive studies in people with diabetes to show clear superiority of one class of antihypertensive drugs over another. The majority of the beneficial effects on cardiovascular events appear to be related to the antihypertensive actions of these agents. The ONTARGET study was the first to evaluate the effect of combined RAAS blockade in comparison with full-dose ramipril and telmisartan alone [180]. There was no superiority of the ACE inhibitor over the ARB in terms of cardiovascular events, and dual blockade did not confer greater cardiovascular protection and indeed was associated with more adverse events; however, only 30% of all participants in this study had diabetes, and no specific subgroup analysis has been reported so far. Therefore, this study cannot conclusively answer the question of the superiority of different blockers of the RAAS and combination RAAS blockade on microvascular and macrovascular outcomes in diabetes.

Plasma aldosterone levels correlate with the progression of atherosclerosis as assessed in the carotid plaque area [311]. Mineralocorticoid receptor antagonists have been evaluated with respect to cardiovascular outcomes. The Randomized Aldactone Evaluation Study (RALES) study initially showed a beneficial effect of the non-specific aldosterone antagonist spironolactone on mortality [312], but in the more recent Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (EPHESUS) trial [311] a 15% relative risk reduction in all-cause mortality and a 13% relative risk reduction in cardiovascular mortality/complications compared with participants on current standard therapy was demonstrated [313]. Although there is experimental evidence for eplerenone attenuating endothelial dysfunction [311] and early lesion size in experimental models of atherosclerosis [314], the evidence for a direct vasculoprotective effect of these newer agents is awaited, particularly in the context of diabetes.

Inhibitors of neutral endopeptidase (NEP) were associated with unwanted off-target effects, including angioedema [315, 316]. However, more recently the first-in-class combined ARB combined with a neprilysin inhibitor (ARNi) was evaluated for heart failure in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial [317]. Simultaneous inhibition of neprilysin enhanced the NEP system and blockade of the AT_1 receptor with valsartan reduced cardiovascular death and heart failure by 20% and all-cause mortality by 16%. This new class of drugs is a potential effective treatment for heart failure, but the effects in CVD and atherosclerosis need to be further elucidated.

Renal denervation

Initial encouraging results attenuating the overactivity of the sympathetic nervous system in hypertension using renal denervation demonstrated substantial and sustained reductions in blood pressure in people with resistant hypertension [318, 319]. Furthermore, additional beneficial effects were observed, including reductions in serum glucose, insulin, and C-peptide levels three months after denervation [320].

Surprisingly, a randomized clinical trial including a sham control arm (Renal Denervation in Patients with Uncontrolled Hypertension, Symplicity HTN3) did not find superiority of renal denervation compared with the sham control [321]. Many reasons for the failure of this trial have been discussed, including ineffective denervation, inexperience of the operators, and suboptimal medication taking [322]. More recently data from the robustly designed randomized sham-controlled proof-of-concept trials of renal denervation (SPYRAL HTN OFF-MED and SPYRAL HTN ON-MED) involving the next-generation Symplicity Spyral radiofrequency renal denervation system have shown beneficial effects on blood pressure reduction in the renal denervation–treated arm compared to placebo (24 h ambulatory blood pressure −7 vs −3.9 mmHg). It needs to be seen if these blood pressure reductions and associated haemodynamic, hormonal, and metabolic effects will translate into additional or superior vasculoprotection in diabetes [323, 324].

Dyslipidaemia

The lipid profile is usually altered in the diabetic milieu and further altered in the context of liver or renal disease. Dyslipidaemia further accelerates atherosclerosis development and progression (Chapter 48). At any given level of cholesterol, a person with diabetes has a two- to threefold increased cardiovascular risk over a person without diabetes.

Current guidelines based on numerous studies particularly with statins (e.g. Heart Protective Study, HPS [325], Collaborative Atorvastatin Diabetes Study, CARDS [326]) suggest reducing LDL levels <2.5 mmol/l, with some more recent evidence suggesting enhanced benefits if LDL is lowered to <2 mmol/l, triglycerides to <1 mmol/l, and HDL to >1 mmol/l according to pre-existing CVD and risk [327]. This area of research will significantly change with the recent advent of monoclonal antibodies against proprotein convertase subtilisin kexin 9 (PCSK9). These drugs are powerful agents that lower LDL levels by >60%. Furthermore, there have been early reports about beneficial effects on cardiovascular events [328, 329]. Whether there are anti-atherosclerotic effects of these drugs beyond cholesterol lowering, as has been postulated for statins, and efficacy in diabetes needs to be shown in future trials.

Hypercoagulability

Diabetes is associated with pro-thrombotic changes and enhanced coagulability, thus increasing cardiovascular risk [330, 331]. Although not studied in detail, agents such as aspirin may be useful in people with diabetes, with increasing evidence that higher doses of these agents are often required in individuals with diabetes to confer cardiovascular benefits. Other drugs to consider in diabetes are clopidogrel and other agents such as abciximab [332], which has been reported to be particularly effective in people with diabetes.

Novel therapies

Several approaches have been used to intervene in diabetes-associated complications, including aldose reductase inhibitors and PKC isoform inhibitors, in particular PKCβ, but most of the evidence for a potential role for these agents has been obtained in the context of microvascular complications. Furthermore, inhibitors of glucose-induced ROS formation, such as benfotiamine, have been investigated in clinical trials with variable results. AGE inhibitors and RAGE antagonism have also been employed, mainly in the context of diabetic nephropathy. The cross-link breaker alagebrium reduces arterial stiffness in people with hypertension and improves left ventricular function. Direct antagonists of RAGE and human chimeric sRAGE are currently being investigated in early clinical trials, but so far not with respect to macrovascular disease.

Multifactorial approaches

The Steno-2 study, using a multifactorial approach addressing lipids, blood pressure, and hyperglycaemia, demonstrated significant improvements on cardiovascular outcomes [28]. Thus, a synergistic multifactorial approach addressing glycaemic management in the context of additional strategies to reduce concomitant cardiovascular risk factors remains the best approach being currently considered. In terms of glucose lowering, the novel anti-diabetes drugs SGLT-2 inhibitors and GLP-1 receptor agonists have shown cardiovascular benefits and have been included in the new guidelines as preferred anti-diabetes treatments, in particular in individuals with underlying heart failure or CVD. Furthermore, strategies directed towards a reduction in activation of vasoactive systems such as the RAAS, the endothelin and urothelin systems, the AGE/RAGE axis, novel proteins such as TRAIL, and the complement system, in addition to oxidative stress and inflammation, may represent additional promising approaches to prevent and minimize macrovascular disease in diabetes.

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47 Hypertension and Diabetes

Peter M. Nilsson
Lund University, Skåne University Hospital, Malmö, Sweden

Key points

- Hypertension in diabetes is a prevalent and treatable risk factor for cardiovascular complications, nephropathy, and retinopathy.
- Evaluation of hypertension by the use of ambulatory blood pressure monitoring should be offered to all people with type 1 diabetes and type 2 diabetes.
- Most antihypertensive drugs can be used for treatment, but blockers of the renin–angiotensin–aldosterone system (RAAS) may confer special clinical benefits for target organ protection.
- Drug combination therapy is needed for most people to achieve reasonable blood pressure control, even as initial treatment.
- Encouragement of home blood pressure measurements will make it possible to achieve better blood pressure management while also supporting the involvement and empowerment of the person with diabetes.
- According to European guidelines, the blood pressure goal for people with type 2 diabetes is <130/80 mmHg for those younger than 65 years and within a systolic range of 130–140 mmHg for older individuals.

Hypertension often accompanies both type 1 diabetes and type 2 diabetes. The association between the two conditions has long been recognized. In 1923, the Swedish physician Eskil Kylin described a syndrome of diabetes, hypertension, and hyperuricaemia [1], which are now regarded as aspects of the broader 'metabolic syndrome' that has been linked to insulin resistance [2, 3]. The relationship between diabetes and hypertension is complex. Both are common and so are likely to be associated by chance, but in some instances they may have a common cause, even programmed in early life; moreover, hypertension can develop as a consequence of diabetic nephropathy, and some drugs used to treat hypertension can induce diabetes in susceptible individuals, at least at higher dosages.

Hypertension is important because, like diabetes, it is a major cardiovascular risk factor and one that synergizes with the deleterious effects of diabetes. It is also a risk factor for microvascular complications, namely nephropathy and retinopathy. The management of hypertension in diabetes has been widely debated, and there is still a need to agree on treatment targets and strategies. According to European guidelines, the current blood pressure goal for therapy is <130/80 mmHg for those younger than 65 years and within a systolic range 130–140 mmHg for older individuals [4]. During the last 25 years, several well-constructed trials have added considerably to the evidence base [5–8], demonstrating convincingly the benefits of lowering blood pressure, but also highlighting how difficult this can be to achieve in practice.

Size of the problem

Hypertension is widely defined according to the World Health Organization/International Society of Hypertension (WHO/ISH) criteria (Table 47.1). People with diabetes are, however, still at risk of macrovascular and microvascular complications at blood pressure levels below these thresholds, and the treatment target range is therefore lower than 130/80 mmHg for those younger than 65 years (but not lower than 120/70 mmHg) and between a systolic range of 130–140 mmHg for older individuals according to European Guidelines [4].

Overall, hypertension (according to the WHO criteria >140/90 mmHg) is up to twice as common in people with diabetes as in the general population [9]. In white Europeans, 10–30% of people with type 1 diabetes and 60–80% of those with newly diagnosed type 2 diabetes have hypertension [10]. There are racial and ethnic differences in the prevalence of hypertension, which presumably are at least partly genetically determined. For example, hypertension (and macrovascular disease) is less frequent among the Pima and Mexican Americans [11]. Impaired glucose tolerance is also associated with hypertension (20–40% of cases), perhaps reflecting the common origins of these aspects of the metabolic syndrome [12].

The true prevalence of hypertension is increasing in the population with diabetes (especially type 2 diabetes) after allowing for the greater number of cases identified through improved screening and

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Table 47.1 Criteria for hypertension and related tissue damage, defined by the World Health Organization (WHO) and the International Society for Hypertension 1999 [41].

Category	Systolic (mmHg)	Diastolic (mmHg)
WHO criteria for the general population[a]		
Optimal	<120	<80
Normal	<130	<85
High normal	130–139	85–89
Grade 1 hypertension (mild)	140–159	90–99
Subgroup: borderline	140–149	90–94
Grade 2 hypertension (moderate)	160–179	100–109
Grade 3 hypertension (severe)	≥180	≥110
Isolated systolic hypertension	≥140	<90
Subgroup: borderline	140–149	<90
Hypertension-related tissue damage (WHO criteria)		
Grade I: none		
Grade II: subclinical damage (e.g. retinopathy, proteinuria)		
Grade III: clinical damage (e.g. heart failure, ischaemia)		
Degree of proteinuria		
Microalbuminuria: 30–300 mg/24 h (20–200 mg/min)		
Macroalbuminuria: >300 mg/24 h (>300 mg/min)		

[a] Desirable blood pressure limits in people with diabetes are suggested in Figure 47.5.

Table 47.2 Associations between hypertension and diabetes.

- Hypertension associated with type 2 diabetes (insulin resistance or metabolic syndrome)
- Hypertension associated with nephropathy in type 1 diabetes
- Coincidental hypertension in people with diabetes
  - Essential hypertension
  - Isolated systolic hypertension
  - Renal scarring (e.g. from recurrent pyelonephritis)
- Diabetogenic anti-hypertensive drugs
  - Potassium-losing diuretics (chlortalidone, high-dose thiazides)
  - β-blockers (high dosages)
  - Combined diuretics and β-blockers (high dosages)
- Drugs causing obesity, hypertension, and glucose intolerance
  - Glucocorticoids
  - Combined oral contraceptive pills
  - Antipsychotics
- Endocrine disorders causing hypertension and glucose intolerance
  - Acromegaly
  - Cushing syndrome
  - Conn's syndrome
  - Phaeochromocytoma

the lowering of thresholds for treatment of blood pressure [13]. The causes probably include the rising prevalence of obesity and improved survival of older people with diabetes.

Causes of hypertension in diabetes

Associations between hypertension and diabetes are listed in Table 47.2. Essential hypertension and isolated systolic hypertension are both common in people without diabetes, especially in older people. It is estimated that essential hypertension accounts for about 10% of cases in people with diabetes. Other important causes are the hypertension that coexists with insulin resistance, obesity, and impaired glucose tolerance in the metabolic syndrome, and hypertension secondary to diabetic nephropathy, as discussed in detail in what follows.

Hypertension in the metabolic syndrome

This syndrome comprises insulin resistance, impaired fasting glycaemia (including type 2 diabetes), a characteristic dyslipidaemia – hypertriglyceridaemia, low high-density lipoprotein (HDL) cholesterol, and somewhat raised low-density lipoprotein (LDL), with a clear excess of small, dense LDL particles – truncal obesity, procoagulant changes (raised plasminogen activator inhibitor 1 and fibrinogen levels), and hyperuricaemia [2, 14, 15]. As these abnormalities are all risk factors for atherogenesis, the syndrome is associated with a marked tendency for early vascular ageing, leading to macrovascular disease, especially coronary heart disease (CHD) and stroke (Figure 47.1). As discussed in Chapter 17, insulin resistance has been proposed by Reaven [2], DeFronzo and Ferrannini [14], and others [15] to be a fundamental cause of hypertension and cardiovascular disease (CVD) in addition to type 2 diabetes. Insulin resistance is partly genetically determined, while acquired factors such as obesity, physical inactivity, and perhaps malnutrition *in utero* and weight changes during early infancy may also contribute [16]. In support of the latter, family studies have revealed a correlation between the blood pressure of the mother and her offspring that appears to be non-hereditary in origin; early growth retardation may programme abnormal development of the vasculature and also the tissues that regulate glucose homeostasis. This could in turn be influenced by maternal genes for raised blood pressure that will not only programme the blood pressure of the offspring, but also may influence fetal growth retardation and a lower birth weight as a side phenomenon [17].

Insulin resistance is closely associated with high blood pressure in both humans and animals. Experimental induction of insulin resistance (e.g. feeding rats with fructose) is accompanied by a rise in blood pressure. More persuasively, an inverse relationship has been demonstrated in humans between blood pressure levels and insulin sensitivity [18] (Figure 47.2). Various mechanisms have been proposed to explain how insulin resistance and/or the accompanying hyperinsulinaemia could increase blood pressure (Figure 47.3). First, insulin is an endothelium-dependent vasodilator, releasing nitric oxide (NO) from the endothelium, which relaxes vascular smooth muscle [19]; blunting of this effect, caused by insensitivity to the action of insulin on the endothelium and also on metabolically important tissues, could contribute to the increased peripheral resistance that is the hallmark of hypertension in obesity and type 2 diabetes. Impaired endothelium-mediated vasodilation is associated with insulin-resistant states and may have a key role in the initiation and progression of atherosclerosis [20], further negatively influenced by smoking.

By contrast, insulin also has several actions that tend to raise blood pressure, and these are accentuated in insulin-resistant states, presumably because sensitivity to the effects of the raised insulin levels is preserved. Insulin acts on the distal renal tubule to retain Na^+ ions and water [20, 21], an effect that still operates in people with insulin resistance [22], and so could contribute to

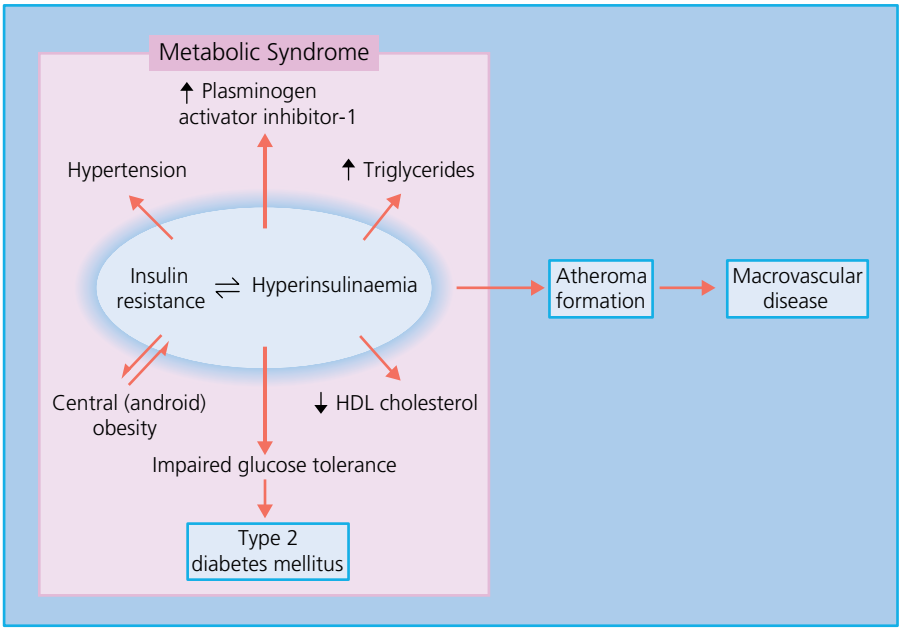

Figure 47.1 The metabolic syndrome. HDL, high-density lipoprotein.

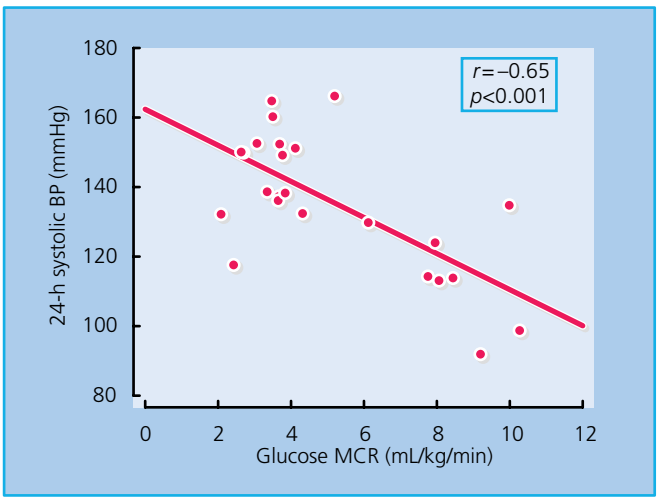

Figure 47.2 Hypertension is associated with insulin resistance. Insulin sensitivity, measured as the metabolic clearance rate (MCR) of glucose during an insulin clamp study, is inversely related to the mean 24 h systolic and ambulatory blood pressure (BP). Source: Pinkney et al. 1994 [18]. Reproduced with permission from Wolters Kluwer Health.

the rise in total body Na^+ content that occurs in obesity and type 2 diabetes [23]. Insulin also stimulates the cell membrane Na^+–K^+ ATPase, which would raise intracellular Na^+ concentrations in vascular smooth muscle and, by increasing systolic Ca^{2+} levels, would enhance contractility and increase peripheral resistance [22, 23]. Through its effects on the central nervous system (CNS), insulin may stimulate the sympathetic outflow. Theoretically, this could also increase blood pressure, although direct evidence in humans is lacking [22, 24]. Finally, insulin may stimulate the proliferation of vascular smooth muscle cells, which could lead to medial hypertrophy and increased peripheral resistance [22, 25].

Hypertension and diabetic nephropathy

This association is most obvious in young people with type 1 diabetes, in whom the presence of hypertension is strikingly related to renal damage and even minor degrees of proteinuria. Blood pressure begins to rise when the urinary albumin excretion (UAE) enters the microalbuminuric range (>30 mg/24 h) and is usually over the WHO threshold when UAE reaches the macroalbuminuric stage (>300 mg/24 h) [26]. The association may be partly genetically determined: people with diabetes and microalbuminuria commonly have parents with hypertension and may also inherit overactivity of the cell membrane Na^+–H^+ pump (indicated by increased Na^+–Li^+ counter-transport in red blood cells), which would tend to raise intracellular Na^+ concentrations and thus increase vascular smooth muscle tone [27].

The basic mechanisms of hypertension include decreased Na^+ excretion with Na^+ and water retention. Peripheral resistance is increased, to which raised intracellular Na^+ will contribute. The role of the renin–angiotensin–aldosterone system (RAAS) is uncertain, as both increased and decreased activity have been reported [28, 29]. These discrepancies may be explained by differences in diet, treatment, metabolic management, and the type and duration of diabetes. Na^+ retention and hypertension would be predicted to suppress the RAAS, whereas renin levels may be influenced by other complications of diabetes: renal tubular acidosis type 4 causes hyporeninaemic hypoaldosteronism and neuropathy can also lower plasma renin, while renin may be raised in retinopathy and advanced nephropathy. Individuals with microalbuminuria who are insulin resistant appear to be particularly susceptible to hypertension [30].

Impact of hypertension in diabetes

A large proportion of people with hypertension and diabetes show signs of cardiovascular aging and target-organ damage [10]. Hypertension, as an independent risk factor for atherogenesis, synergizes with the effects of diabetes and significantly increases the development and progression of CHD and cerebrovascular and

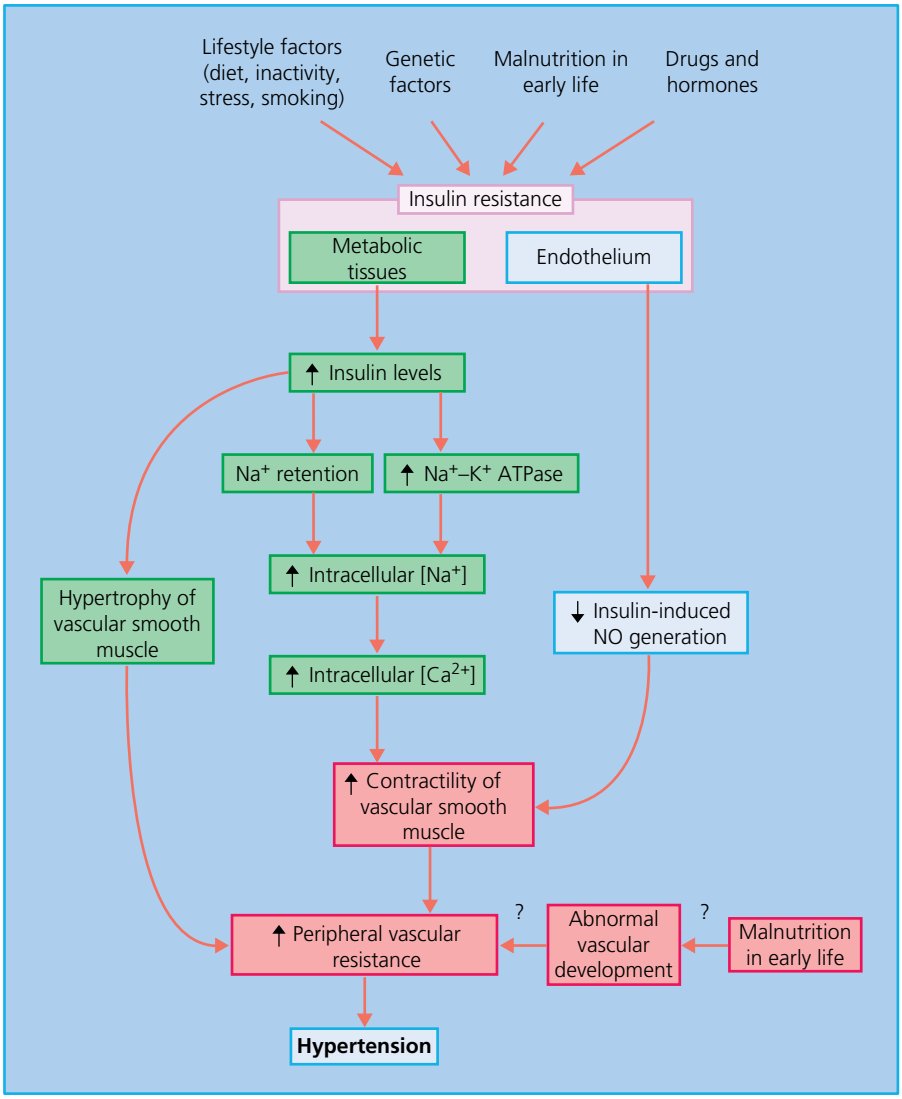

Figure 47.3 Possible mechanisms of hypertension in conditions of insulin resistance. NO, nitric oxide.

peripheral vascular disease. Overall, the effects of hypertension on deaths from CHD are increased two- to fivefold in people with diabetes, with the greatest relative increase occurring at the lowest blood pressure levels (Figure 47.4).

The deleterious effects of hypertension on left ventricular function are also accentuated by the presence of diabetes. These include impaired left ventricular relaxation [31] and increased left ventricular mass [32], the latter being an independent predictor of premature death from CHD.

Hypertension also predisposes to the development of certain microvascular complications, particularly nephropathy and end-stage renal disease, for which the risk is increased two- to threefold (Chapter 44). In addition, hypertension is also a risk factor for retinopathy, as has been confirmed by the beneficial effects of improved blood pressure management in people with type 2 diabetes reported by the UK Prospective Diabetes Study (UKPDS) [5].

In recent years, interest in arterial stiffness (arteriosclerosis) has increased, as this is a characteristic of people with the metabolic syndrome and type 2 diabetes [33]. Increased aortic pulse wave velocity (aPWV) is a marker of the arterial stiffness that is supposed to precede, but later also to interact with, atherosclerosis [34]. A threshold of aPWV >10 m/s [35] is a marker of increased arterial stiffness that can also independently predict cardiovascular risk and total mortality [36]. At early stages, the degree of hyperglycaemia and dyslipidaemia also increases arterial stiffness in people with normoglycaemia or impaired glucose metabolism [37], resulting in early vascular ageing [38]. In fact, arterial stiffness is even a predictor of type 2 diabetes in a general middle-aged population [39].

Screening for hypertension in diabetes

As the two conditions are so commonly associated, people with diabetes must be regularly screened for hypertension and vice versa. People with hypertension, especially if they have obesity or are receiving treatment with potentially diabetogenic drugs, should be screened for diabetes at diagnosis and during follow-up. Should hyperglycaemia be detected, potentially diabetogenic antihypertensive drugs should be reduced or changed to others or used in combinations that do not further impair glucose tolerance; normoglycaemia can then often be restored when lifestyle improvements are also supported.

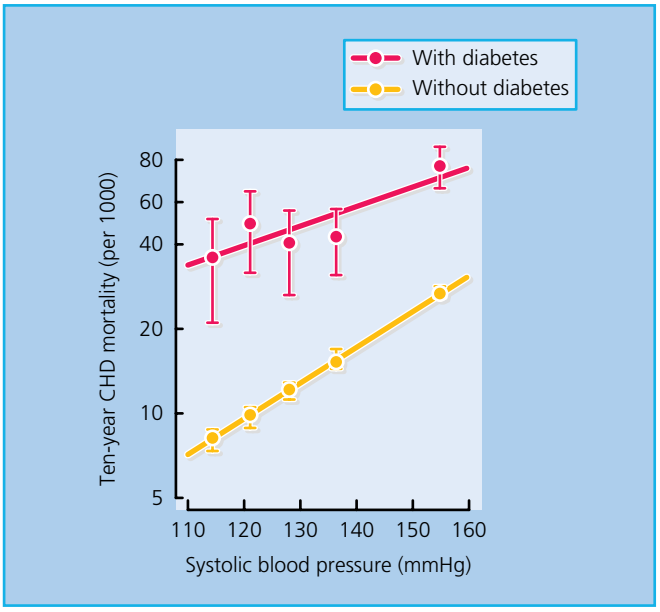

Figure 47.4 Synergistic effects of diabetes and hypertension on deaths from coronary heart disease (CHD). Data from 342 815 people without diabetes and 5163 people with diabetes aged 35–57 years, free from myocardial infarction at entry. Source: Reproduced with permission from O. Vaccaro, paper presented at the 26th Annual Meeting of the European Diabetes Epidemiology Group, Lund, 1991.

All people with diabetes should have their blood pressure checked at diagnosis and at least annually thereafter. This is especially important in those with other cardiovascular risk factors, such as nephropathy (which is associated with a substantial increase in the cardiovascular mortality rate), obesity, dyslipidaemia, smoking, or elevated glycated haemoglobin (HbA_{1c}), or with a positive family history of early-onset cardiovascular disease.

Measurement of blood pressure

Blood pressure should be measured with the individual in the supine or sitting position, with an accurate sphygmomanometer and a cuff of appropriate size (i.e. wider for people with obesity and an arm circumference of >32 cm). Systolic and diastolic blood pressure should be recorded, to the nearest 2 mmHg if using a manual sphygmomanometer, from phases I and V (i.e. appearance and final disappearance of the sounds of Korotkoff). Usual precautions should be taken to ensure reliability and avoid 'white coat' stress effects, which can acutely raise blood pressure. Conditions should be quiet and relaxed, and at least two readings should be taken initially and then repeated at intervals over weeks or months to determine the person's typical values and any trend towards change. Office blood pressure could be complemented by repeated home blood pressure recordings.

Blood pressure should also be checked with the individual in the upright position (one minute after standing), because there may be a significant postural fall (>20 mmHg systolic) in people with autonomic neuropathy, older people, or those treated with vasodilators or diuretics. Marked postural hypotension, which can coexist with supine hypertension, may indicate the need to change or reduce antihypertensive medication, especially if symptoms are provoked.

Ambulatory blood pressure monitoring over 24 hours may be useful in some cases to exclude 'white coat' effects, and in people with early nephropathy who have nearly normal blood pressure during the day, but who may be at risk of hypertensive tissue damage because they do not have the physiological blood pressure dip during sleep. Masked hypertension (non-dipping at night) is also a common phenomenon in about 20–30% of all individuals with type 2 diabetes [40].

Diagnosis of hypertension in diabetes

The criteria issued in 1999 by the WHO and ISH define hypertension as an office blood pressure exceeding 140/90 mmHg (Korotkoff I-V) and borderline hypertension as being below these limits but above 130 mmHg systolic and/or 85 mmHg diastolic (Figure 47.5) [41]. Established hypertension is diagnosed when readings consistently exceed 140/90 mmHg over several weeks, or when the blood pressure is very high (diastolic blood pressure >110 mmHg), or when there are clinical signs of tissue organ damage from long-standing hypertension.

It is clear from numerous epidemiological studies that the WHO/ISH threshold is sometimes too high in people with diabetes because of their additional risk of both macrovascular and microvascular disease [42], and that there are definite benefits from treating people with microalbuminuria whose diastolic blood pressure is <90 mmHg. Various other expert bodies have suggested alternative, generally lower target levels (Figure 47.5). A consensus would be to aim for a blood pressure below 130/80 mmHg for those

Treatment strategies in people with diabetes

Recommendations	Class	Level
Antihypertensive drug treatment is recommended for people with diabetes when office BP is ≥140/90 mmHg.	I	A
In people with diabetes receiving BP-lowering drugs it is recommended:		
• To target SBP to 130 mmHg and lower, if tolerated, but not lower than 120 mmHg.	I	A
• In older people (aged ≥65 years), to target to a SBP range of 130 to <140 mmHg.	I	A
• To target the DBP to < 80 mmHg, but not lower than 70 mmHg.	I	C
It is recommended to initiate treatment with a combination of an RAAS blocker with a CCB or thiazide/thiazide-like diuretic.	I	A
Simultaneous administration of two RAAS blockers, e.g. an ACE inhibitor and ARB, is not indicated.	III	A

Figure 47.5 Treatment strategies for people with diabetes according to 2018 European Society of Cardiology/European Society of Hypertension guidelines for the management of arterial hypertension. BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; RAAS, renin-angiotensin-aldosterone system; CCB, calcium channel blocker; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker. Source: Reproduced by permission from Williams et al. 2018 [4].

younger than 65 years (but not lower than 120/70 mmHg) and within a systolic range of 130–140 mmHg for older people according to European [4, 43] and international guidelines [44, 45].

Investigation of hypertension in diabetes

Initial investigation of the person with diabetes and hypertension aims to exclude rare causes of secondary hypertension (Table 47.2), to assess the extent of tissue organ damage caused by hypertension and diabetes (Table 47.1), and to identify other potentially treatable risk factors for vascular disease. The major points in the medical history and examination are shown in Table 47.3:

- *Cardiac function*. A standard 12-lead electrocardiogram may show obvious ischaemia, arrhythmia, or left ventricular hypertrophy; the last is more accurately demonstrated by echocardiography, which will also reveal left ventricular dysfunction and decreased ejection fraction. Exercise testing or stress-echo testing and 24 h Holter monitoring may also be appropriate.
- *Renal function*. A fresh urine sample should be tested for microalbuminuria (Chapter 44) and another examined microscopically for red and white blood cells, casts, and other signs of renal disease. Microscopic haematuria can occasionally occur in people with type 1 diabetes (particularly children) in the apparent absence of significant renal dysfunction, but coexisting renal disease must always be excluded. Serum urea, creatinine, and electrolytes should be checked. If the serum creatinine concentration is raised, measurement of the glomerular filtration rate should be considered, ideally using a specific clearance method such as using chromium–ethylenediaminetetraacetic acid complex (Cr-EDTA), iohexol, or cystatin C. Further specialist investigations include an isotope renogram and other tests for renal artery stenosis (Figure 47.6). This complication of renal arterial atherosclerosis may affect up to 20% of older people with type 2 diabetes and, if bilateral, can lead to severe and sometimes permanent renal impairment if angiotensin-converting enzyme (ACE) inhibitors are given.
- *Lipid profile*. Fasting serum lipid concentrations should be checked. If total cholesterol or triglyceride levels are found to be elevated after repeated measurements, further investigation of lipoprotein subclasses – very low-density lipoprotein (VLDL), LDL, HDL, and also the apo-B-to-apo-A1 lipoprotein ratio – is recommended. Treatment for hyperlipidaemia should be considered if the total cholesterol is >4.0 mmol/l, the LDL cholesterol level is >2.5 mmol/l, or the LDL-to-HDL cholesterol ratio is >4, and with stricter targets according to European guidelines [43]. This is discussed in more detail in Chapters 48, 49, and 51.

Other forms of secondary hypertension may be indicated by clinical findings of endocrine or renal disease, significant hypokalaemia (plasma potassium <3.5 mmol/l without previous diuretic treatment), failure of hypertension to respond to standard treatment, or a sudden decline in glomerular filtration rate after starting treatment with ACE inhibitors (suggestive of renal artery stenosis).

Management of hypertension in diabetes

Strict blood pressure control is the primary goal of treatment. In recent years, target treatment levels have been lowered progressively to the current recommendation of a mean office blood

Table 47.3 Investigation of the person with diabetes and hypertension.

Investigations	
History	Is hypertension significant?
Cardiovascular symptoms	Does hypertension have an underlying cause?
Previous urinary disease	• Renal
Smoking and alcohol use	• Endocrine
Medication	• Drug-induced
Family history of hypertension or cardiovascular disease	Has hypertension caused tissue damage?
Examination	• Left ventricular hypertrophy
Blood pressure erect and supine	• Ischaemic heart disease
Left ventricular hypertrophy	• Cardiac failure
Cardiac failure	• Peripheral vascular disease
Peripheral pulses (including renal bruits and radiofemoral delay)	• Carotid plaque
Ankle–brachial index	• Renal impairment
Fundal changes of hypertension	• Fundal changes
Evidence of underlying endocrine or renal disease	Are other cardiovascular risk factors present?
Electrocardiography	• Smoking
Left ventricular hypertrophy	• Hyperlipidaemia
Ischaemic changes	• Elevated glycated haemoglobin (HbA_{1c})
Rhythm	• Positive family history of cardiovascular disease
Chest radiography	• Signs of cognitive impairment
Cardiac shadow size	
Left ventricular failure	
Echocardiography	
Left ventricular hypertrophy	
Dyskinesia related to ischaemia	
Blood tests	
Urea, creatinine, electrolytes	
Fasting lipids	
Urinary tests	
(Micro-)albuminuria	

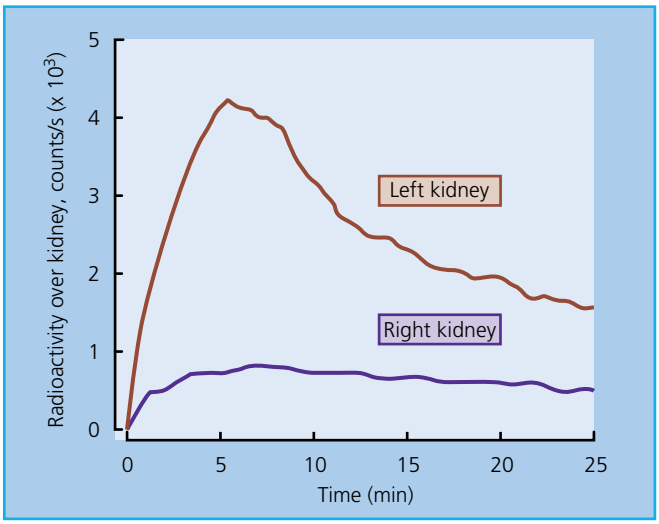

Figure 47.6 Renal artery stenosis affecting the right kidney in a person with diabetes and hypertension. Uptake of the isotope on this side is markedly reduced and delayed.

pressure below 130/80 mmHg for those younger than 65 years and within a systolic range of 130–140 mmHg for older individuals and for all people who can tolerate these levels without side effects, such as orthostatic reactions or compromising arterial circulation in critical vascular beds. Recent observations indicate that there may be subgroups of susceptible individuals who will not tolerate a dramatic reduction below 130 mmHg systolic blood pressure, and so caution should be exercised, especially when comorbidities are present. A blood pressure reduced below 120/70 mmHg may impair the coronary circulation in susceptible individuals.

Management begins with lifestyle modification, but few people respond to this alone, and most will require more than one antihypertensive drug, potentially as a single tablet fixed drug combination [4] from treatment initiation to manage blood pressure adequately, a fact that new guidelines emphasize [4, 43–45].

Non-pharmacological treatment

The treatment of hypertension in people with diabetes must be based on structured lifestyle intervention. This means weight reduction or weight stabilization in those with obesity, sodium restriction, diet modification, and regular physical exercise (moderate intensity, 40–60 minutes, 2–3 times weekly). Dietary saturated fat intake has been associated with impaired insulin sensitivity and should therefore be reduced [46]. Alcohol should be restricted to 2–3 units/d in men and 2 units/d in women, but omitted altogether if hypertension proves difficult to manage. It should be remembered that the Look AHEAD (Action for Health in Diabetes) study in the USA provided no evidence for benefits of weight loss *per se* as a strategy to lower cardiovascular risk and reduce mortality in individuals with obesity and type 2 diabetes of long duration, even though glucose and other risk factors may improve [47]. This underlies the rationale to aim for control of conventional cardiovascular risk factors in the first place, rather than weight loss itself, with drugs based on evidence and according to guidelines [4, 43–45].

Smoking causes an acute increase in blood pressure and greater variability overall [48]. Smoking cessation is especially important, as smoking not only accelerates the progression of atherosclerosis and vascular ageing, but also impairs insulin sensitivity [49] and worsens albuminuria [50]. Drug treatment with nicotine supplementation for 4–6 weeks (chewing gum or patches), bupropion, or varenicline (not available in Europe) may be useful.

When adopted in full, lifestyle modification can be effective for blood pressure control itself and is believed to benefit cardiovascular risk in general, even if the evidence is scanty. The measures mentioned can lower systolic and diastolic blood pressure by up to 11 and 8 mmHg, respectively [51], as much as many antihypertensive drugs, and sometimes enough to lessen the need for drug therapy. Weight reduction in those with obesity can similarly reduce blood pressure, but not cardiovascular events, according to the Look AHEAD study, which is why more research is needed [47]. It should be remembered that if target-organ damage is present, lifestyle advice is not enough and drug therapy should be considered.

Antihypertensive drug therapy

Numerous drugs are available to lower blood pressure, but some are better suited than others to the particular needs of people with diabetes because of their favourable or neutral effects on glucose metabolism and other factors. Most people with diabetes (at least two-thirds) will require combinations of antihypertensive drugs to control blood pressure, with an average of around three different drugs in two large studies [5, 6]. Accordingly, the clinician must be able to use a wide variety of antihypertensive drugs and to choose combinations that exploit pharmacological synergy. Combination therapy usually means that lower dosages of individual drugs can be used, thus reducing the risk of adverse effects.

Diuretics

Diuretics are often effective antihypertensive agents for people with diabetes, in whom the total body sodium load is increased and the extracellular fluid volume expanded [52]; however, diuretics that increase urinary potassium and magnesium losses can worsen hyperglycaemia, as insulin secretion is impaired by potassium depletion, and insulin sensitivity in peripheral tissues may also be decreased [53]. The use of high-dose thiazide diuretics, equivalent to ≥5 mg/d bendroflumethiazide (bendrofluazide), increases the risk of people with hypertension developing diabetes by up to threefold; this does not seem to occur with low dosages (up to 2.5 mg/d bendroflumethiazide) [54]. Potassium depletion is particularly severe with high-dose chlortalidone (chlorthalidone), less so with furosemide (frusemide) and bendroflumethiazide, and apparently negligible with indapamide. This mechanism is irrelevant to those with C-peptide–negative type 1 diabetes who are totally dependent on exogenous insulin. Thiazides may also aggravate dyslipidaemia [55], although low dosages probably carry a small risk. Thiazides have also been associated with gout and erectile dysfunction and are therefore generally avoided in middle-aged men with diabetes and hyperuricaemia or erectile dysfunction; nevertheless, some evidence suggests that the risk of erectile failure may have been overstated. Diuretics may precipitate hyperosmolar hyperglycaemic syndrome and should be avoided or used at the lowest effective dose in people with a history of this complication.

Diuretics prevent CVD in older people with type 2 diabetes and systolic hypertension [56], but one observational study suggested that the use of diuretics increased cardiovascular mortality in those with hypertension and type 2 diabetes who remain hyperglycaemic in spite of treatment [57]. Overall, these drugs are effective and safe when used appropriately in people with diabetes.

Diuretics suitable for use in diabetic hypertension include furosemide, bendroflumethiazide (≤2.5 mg/d), hydrochlorothiazide, spironolactone, and indapamide. Low dosages should be used, sometimes in combination with potassium supplements or potassium-sparing drugs, such as amiloride. If ineffective, diuretics should be combined with another first-line drug (e.g. an ACE inhibitor or an angiotensin II receptor blocker [ARB]), rather than given at increased dosage. Spironolactone is best not combined with an ACE inhibitor, as this increases the risk of hyperkalaemia. Furosemide is useful in people with renal impairment (serum creatinine >150 µmol/l) or oedema.

Serum urea, creatinine, and potassium should be checked when starting diuretic therapy and every 6–12 months thereafter, as dangerous disturbances in plasma potassium concentration can develop, especially in individuals with diabetes and renal impairment.

β-Adrenergic blocking agents

β-receptor blockers may significantly lower blood pressure in people with diabetes and hypertension, even though renin release (a major target for these drugs) is commonly reduced in diabetes

because of Na^+ and fluid retention. These drugs are often ineffective in Afro-Caribbean people, who commonly have low renin hypertension. Other mechanisms of action that reduce blood pressure include reductions in heart rate and cardiac output via interaction with β_1- and β_2-receptors in the myocardium and in the vessel wall.

Like diuretics, β-receptor blockers may aggravate both hyperglycaemia and dyslipidaemia [58]. These effects depend on both the dosage and the degree of selectivity of the individual drug. The hyperglycaemic effect is attributed to inhibition of β_2-adrenergic–mediated insulin release and decreased insulin action in peripheral tissues; the long-term risk for a person without diabetes developing the disease may be increased sixfold [59], and even more if given together with thiazides. Some studies suggest that the hazards of both hyperglycaemia and hyperlipidaemia have been exaggerated and may be both dose dependent and secondary to weight gain [60]. The metabolic side effects of β-blockers can be reduced by using low dosages combined with other agents, particularly dihydropyridine calcium-channel antagonists, or by intensifying non-pharmacological efforts to decrease weight and improve physical activity.

β-blockers have other side effects relevant to diabetes. They may interfere with the counter-regulatory effects of catecholamines released during hypoglycaemia, thereby blunting manifestations such as tachycardia and tremor and delaying recovery from hypoglycaemia [61]. In clinical practice, however, this rarely presents a serious problem, especially when cardioselective β_1-blockers are used. β-blockers may also aggravate erectile dysfunction and are generally contraindicated in second- or third-degree atrioventricular heart block, severe peripheral vascular disease, asthma, and chronic airway obstruction. Certain β-blockers such as metoprolol and carvedilol [62, 63] can be used favourably in cardiac failure in people with diabetes, as shown in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) study, in which 25% of the participants had diabetes [62].

Atenolol is a commonly used drug, as it is cardioselective and water soluble, which reduces CNS side effects and renders its metabolism and dosage more predictable. It is mostly effective as a single daily dose, which probably encourages medication taking as prescribed. In the UKPDS, its effect was comparable to that of the ACE inhibitor captopril [64]; however, it should be kept in mind that the stroke-preventive effect of atenolol is 16% less than that of other antihypertensive drugs, based on data from meta-analyses. Metoprolol is an alternative, in moderate dosages. Both non-selective and selective β-blockers are effective in the secondary prevention of myocardial infarction after an initial event in people with diabetes [65]. Metoprolol or carvedilol may be indicated in those who also have heart failure [62, 63], and β-blockers in general are useful in individuals who suffer from angina or tachyarrhythmias.

Calcium-channel antagonists

These useful vasodilator agents do not generally worsen glycaemia when used at conventional dosages, although sporadic cases of hyperglycaemia have been reported after starting a calcium-channel antagonist of the dihydropyridine class [66]. This may be caused by inhibition of insulin secretion (a calcium-dependent process) in susceptible individuals, or a compensatory sympathetic nervous activation, which antagonizes both insulin secretion and action following vasodilatation.

Calcium-channel antagonists have a slight negative inotropic effect and are contraindicated in significant cardiac failure; they often cause mild ankle oedema, but this is caused by relaxation of the peripheral pre-capillary sphincters and raised capillary pressure rather than by right ventricular failure. Because of their potent vasodilator properties, these drugs can cause postural hypotension and can aggravate that brought about by autonomic neuropathy. Non-dihydropyridine calcium-channel antagonists (e.g. verapamil) reduce proteinuria in diabetic nephropathy, but this effect is not seen with dihydropyridine derivatives, such as nifedipine, amlodipine, felodipine, and isradipine [67].

Because of their other cardiac actions, these drugs are particularly indicated in people with hypertension who also have angina (e.g. sustained-release nifedipine and diltiazem) or supraventricular tachycardia (e.g. verapamil). Their vasodilator properties may also be beneficial in peripheral vascular disease. Calcium-channel antagonists are ideally combined with selective β_1-blockers, but the specific combination of verapamil and β-blockers (especially together with digoxin) must be avoided because of the risk of conduction block and asystole. Overall, calcium-channel antagonists appear less or similarly cardioprotective, but better at preventing stroke, than either β-blockers or thiazide diuretics [68, 69].

Amlodipine given once daily is an evidence-based and convenient preparation for general use, and felodipine, isradipine, and sustained-release nifedipine are suitable alternatives.

Angiotensin-converting enzyme inhibitors

ACE inhibitors may be used in diabetes-related hypertension, even in cases where the general RAAS is not activated, as the drugs may interfere with local angiotensin action in specific target tissues. When used alone, however, these agents have a limited hypotensive action in many Afro-Caribbean people, who tend to have suppressed RAAS activity.

ACE inhibitors have no adverse metabolic effects and may even improve insulin sensitivity [70]; hypoglycaemia has rarely been reported [71]. These drugs are particularly beneficial in diabetic nephropathy by reducing albuminuria and possibly delaying progression of renal damage [72]. Their antiproteinuric effect may be caused specifically by relaxation of the efferent arterioles in the glomerulus, which are highly sensitive to vasoconstriction by angiotensin II, thus reducing the intraglomerular hypertension that is postulated to favour albumin filtration; however, the importance of this mechanism remains controversial [73]. ACE inhibitors are also indicated in cardiac failure, in combination with relatively low dosages of diuretics.

A dry cough is reported by 10–15% of people treated with ACE inhibitors (more commonly in women than in men), because these drugs also interfere with the breakdown of kinins in the bronchial epithelium. Changing to another ACE inhibitor or an ARB may avoid this problem. ACE inhibitors occasionally precipitate acute renal failure, particularly in older people and in individuals taking non-steroidal anti-inflammatory drugs (NSAIDs), or who have bilateral renal artery stenosis. Other side effects (rashes, neutropaenia, taste disturbance) are unusual with the low dosages currently recommended, but become more prominent in renal failure. Because ACE inhibitors cause potassium retention, they should not generally be taken concurrently with potassium-sparing diuretics (spironolactone and amiloride) or potassium supplements. Serum creatinine and potassium levels should be monitored regularly,

especially in individuals with renal failure or type 4 renal tubular acidosis, in whom hyperkalaemia can rapidly reach dangerous levels. RAAS-blocking drugs should not be used in pregnant women, or fertile women without contraceptives, due to their teratogenic effects.

Ramipril, enalapril, lisinopril, and perindopril, given once daily for hypertension, are all well-established ACE inhibitors that are suitable for use in people with diabetes. The first dose of an ACE inhibitor should be small and taken just before bedtime to minimize postural hypotension, which may be marked in people receiving diuretics or on a strict sodium-restricted diet. The same problem may arise in those with autonomic neuropathy. ACE inhibitors are recommended in people with left ventricular dysfunction following myocardial infarction (Chapters 49 and 50). Ramipril has been shown to prevent cardiovascular morbidity and mortality in high-risk people with diabetes, with or without pre-existing ischaemic heart disease [74].

Angiotensin II type 1 receptor blockers

This class includes losartan, irbesartan, valsartan, candesartan, and telmisartan, which act on the AT_1 receptor to block it and thereby decrease blood pressure. They are metabolically neutral [75] and, unlike the ACE inhibitors, do not cause cough. They are effective antihypertensive drugs in people with diabetes [76] and slow the progression of nephropathy in those with diabetes and varying degrees of albuminuria (in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan [RENAAL], Irbesartan Diabetic Nephropathy Trial [IDNT], and Irbesartan in Patients with Type 2 diabetes and Microalbuminuria [IRMA-2] studies) [77–79]. Losartan has also been shown in a subgroup of the Losartan Intervention For Endpoint reduction (LIFE) study to be better than atenolol in reducing both cardiovascular endpoints (by 25%) and total mortality (by 40%) in high-risk people with type 2 diabetes with hypertension and left ventricular hypertrophy [80]. Interestingly, the combination of an ACE inhibitor (lisinopril) with an AT_1 antagonist (candesartan) was more effective than either agent alone in lowering blood pressure and UAE in people with type 2 diabetes [81]; however, in the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) study, no extra benefits were recorded for the combination of telmisartan and ramipril on cardiovascular endpoints compared with monotherapy [82]. The combination of an ACE inhibitor and an AT_1 receptor blocker for treatment of hypertension is discouraged owing to the negative interaction and risk of adverse renal effects, as evident from the ONTARGET study [83].

Direct renin inhibitor

Another approach to block RAAS is via direct renin inhibition. In the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) study, this strategy was not successful when the renin inhibitor aliskiren was combined with either an ACE inhibitor or an AT_1 receptor blocker versus placebo for cardiovascular and renal protection [84]. As a result, this combination is not recommended for people with type 2 diabetes, hypertension, and microalbuminuria in current European guidelines [4].

α1-adrenoceptor antagonists

α_1-blockers can lower blood pressure effectively and also improve dyslipidaemia and insulin sensitivity. Doxazosin is normally well tolerated, especially in combination therapy; side effects include nasal congestion and postural hypotension. Doxazosin has been reported to be inferior to the diuretic chlortalidone in the prevention of stroke and heart failure [85].

Treatment strategies

In general, lifestyle modification should be tried initially for ~3 months. If moderate hypertension (systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg) or signs of hypertensive tissue damage are present, then drug therapy should be started at the outset. Initially, monotherapy with one of the first-line drugs suggested should be used, or even as a fixed drug combination at initiation of treatment, the choice being influenced by other factors such as coexistence of angina, heart failure, or nephropathy. All drug treatment should be evidence based and cost-effective in the individual. A move to combination drug treatment is recommended for many people owing to the high prevalence of target-organ damage when early blood pressure control is mandatory [4, 43–45].

Hypertension in type 1 diabetes

ACE inhibitors are especially suitable if the individual has albuminuria or more advanced stages of diabetic nephropathy. Diuretics, β_1-selective blockers, and calcium-channel antagonists are equally valid alternatives with regard to blood pressure reduction.

If renal function is moderately impaired (serum creatinine values >150 μmol/l), thiazide diuretics become less effective, and furosemide or other loop diuretics should be used instead; however, in established end-stage renal disease (serum creatinine >500 μmol/l), furosemide may be toxic and dialysis must be started. In some people, hypoglycaemia may be masked by the use of β-blockers.

Hypertension in type 2 diabetes

Blood pressure control is generally more important than the choice of individual drugs. First-line agents, according to evidence from clinical studies, are ACE inhibitors, ARBs, low-dose thiazide diuretics (in older people), furosemide, and calcium-channel antagonists [4, 43–45].

Ramipril has evidence-based support for its use in individuals with type 2 diabetes because of their high cardiovascular risk [74]. β-blockers are second-line drugs for hypertension, but are indicated as secondary prevention (in combination with low-dose aspirin) for those who have had a myocardial infarction, provided that no serious contraindications are present. Low doses of thiazide diuretics are useful in older people with diabetes, as this class of drugs has proven efficacy in preventing stroke and all-cause mortality [8].

α_1-blockers may be used as part of combination therapy, especially in those with dyslipidaemia (high triglycerides and low HDL cholesterol levels) or prostatic hyperplasia. Indapamide is a well-tolerated non-thiazide diuretic and has no metabolic side effects. Spironolactone may also be of value, especially for older obese women with hypertension and hypervolaemia with a low renin profile, even though evidence from large-scale randomized studies is so far lacking.

Combination therapy

Combination therapy is needed in most people with diabetes (especially those with type 2 diabetes) to achieve satisfactory blood pressure management [4, 43–45]. It is often better to use

low-dose combinations than to increase dosages of single agents, as side effects are commonly dose dependent. Potassium-sparing agents (spironolactone and amiloride) should not be combined with an ACE inhibitor, because of the increased risk for hyperkalaemia.

Certain combinations of antihypertensive drugs have proved very safe and effective in low to moderate doses, such as ACE inhibitor plus diuretic, for example in the ADVANCE study with indapamide [86]; calcium-channel antagonists plus ACE inhibitor, for example in the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) study [87]; selective β_1-blocker plus calcium-channel antagonist; or β_1-blocker plus α_1-blocker (less commonly used). In many high-risk individuals, a combination treatment could also be considered as initial therapy, especially when signs of target-organ damage are present.

Some studies have indicated a better diurnal blood pressure control if antihypertensive drugs can be taken at bedtime in persons with type 2 diabetes, especially in so-called non-dippers with elevated nighttime blood pressure [88].

Special considerations in ethnic groups

Hypertension in diabetes represents a serious medical problem in many ethnic groups, such as African Americans. In non-white European individuals, β-blockers and ACE inhibitors are often less effective at lowering blood pressure because the RAAS is already underactive. Diuretics and calcium-channel antagonists are typically drugs to be preferred, particularly in African Americans [89].

Outcome of treating hypertension in diabetes

It is well recognized that effective treatment of hypertension can slow the progression of diabetic nephropathy, lowering UAE and decreasing the rate of fall of the glomerular filtration rate [90]. The assumptions that improved blood pressure management would improve cardiovascular and other prognoses in type 2 diabetes have been confirmed by the UKPDS [5]. In this study, tighter blood pressure levels (averaging 144/82 mmHg) for over eight years led to significant improvements in several outcomes, compared with less strict control that averaged 154/87 mmHg (Table 47.4). Interestingly, the most powerful effects were related to microvascular complications (retinopathy and nephropathy), although significant reductions were also seen in the risk of stroke (44%) and heart failure (56%). Myocardial infarction and peripheral vascular disease showed non-significant reductions (Table 47.4; Figures 47.7 and 47.8).

Overall, therefore, tight blood pressure management provides substantial benefits for people with hypertension and diabetes. Moreover, this treatment strategy seems to be cost-effective, at least according to the health economics analyses in the UKPDS [91]; however, it must be kept in mind that these benefits will not last if a continuous blood pressure reduction cannot be achieved long term, as shown by the 10-year follow-up of the UKPDS [92]. Antihypertensive treatment therefore has to be continued and not interrupted.

Table 47.4 Impact of stricter management of hypertension on diabetes complications, macrovascular disease, and diabetes-related deaths in type 2 diabetes.

Measure	Relative risk with tight control (mean, 95% confidence intervals)	p value
Diabetes-related deaths	0.76 (0.62 to 0.92)	0.19
All-cause mortality	0.82 (0.63 to 1.08)	0.17
Myocardial infarction	0.79 (0.59 to 1.07)	0.13
Stroke	0.56 (0.35 to 0.89)	0.013
Peripheral vascular disease	0.51 (0.19 to 1.37)	0.17
Microvascular disease	0.63 (0.44 to 0.89)	0.009

Source: Data from UKPDS 1998 [5].

Conclusions

The diagnosis, treatment, and follow-up of hypertension are of great importance for the person with diabetes [4, 43–45]. The treatment targets are demanding and require considerable effort from both people with diabetes and healthcare professionals, but the benefits are now undisputed. A modern approach to diabetes care aims at involving and motivating the individual at all stages of treatment for shared decision making and high quality of care [93]. This is also of importance for achieving long-term blood pressure control and a high degree of medication taking.

New antihypertensive drugs are being introduced [94], but fewer now than previously. They have to prove themselves with regard to both efficacy and tolerability. However, some anti-diabetes drugs appear to lower blood pressure in addition to blood glucose [95], but safety concerns are important. SGLT-2 inhibitors lower not only office blood pressure, but also 24 h ambulatory blood pressure, based on a combination of diuretic effects, weight loss, and other less well-understood mechanisms [96, 97].

In the future, the application of cardiovascular genomics may substantially change the approach to treating hypertension in diabetes [98], aiming at tailoring treatment according to the genotype of the individual (stratified or personalized medicine).

In the ACCORD blood pressure study [99], there was no significant difference in the primary composite outcome of cardiovascular events between participants randomized to achieve a systolic blood pressure goal below 120 mmHg versus below 140 mmHg, even though a reduction in stroke was noticed (secondary endpoint) in the intensive arm. This means that the optimal blood pressure goal for people with hypertension and type 2 diabetes is still not fully established. A recent meta-analysis concluded that among people with type 2 diabetes, blood pressure lowering was associated with improved mortality and other clinical outcomes among those with baseline blood pressure of 140 mmHg and greater, but increased in those with baseline blood pressure below 140 mmHg [100]. In younger people with shorter diabetes duration, fewer comorbidities, and higher estimated risk for stroke and renal events, the blood pressure goal could be at the lower range of 130–140/80–90 mmHg [100–102], and according to European guidelines lower than 130 in those younger than 65 years,

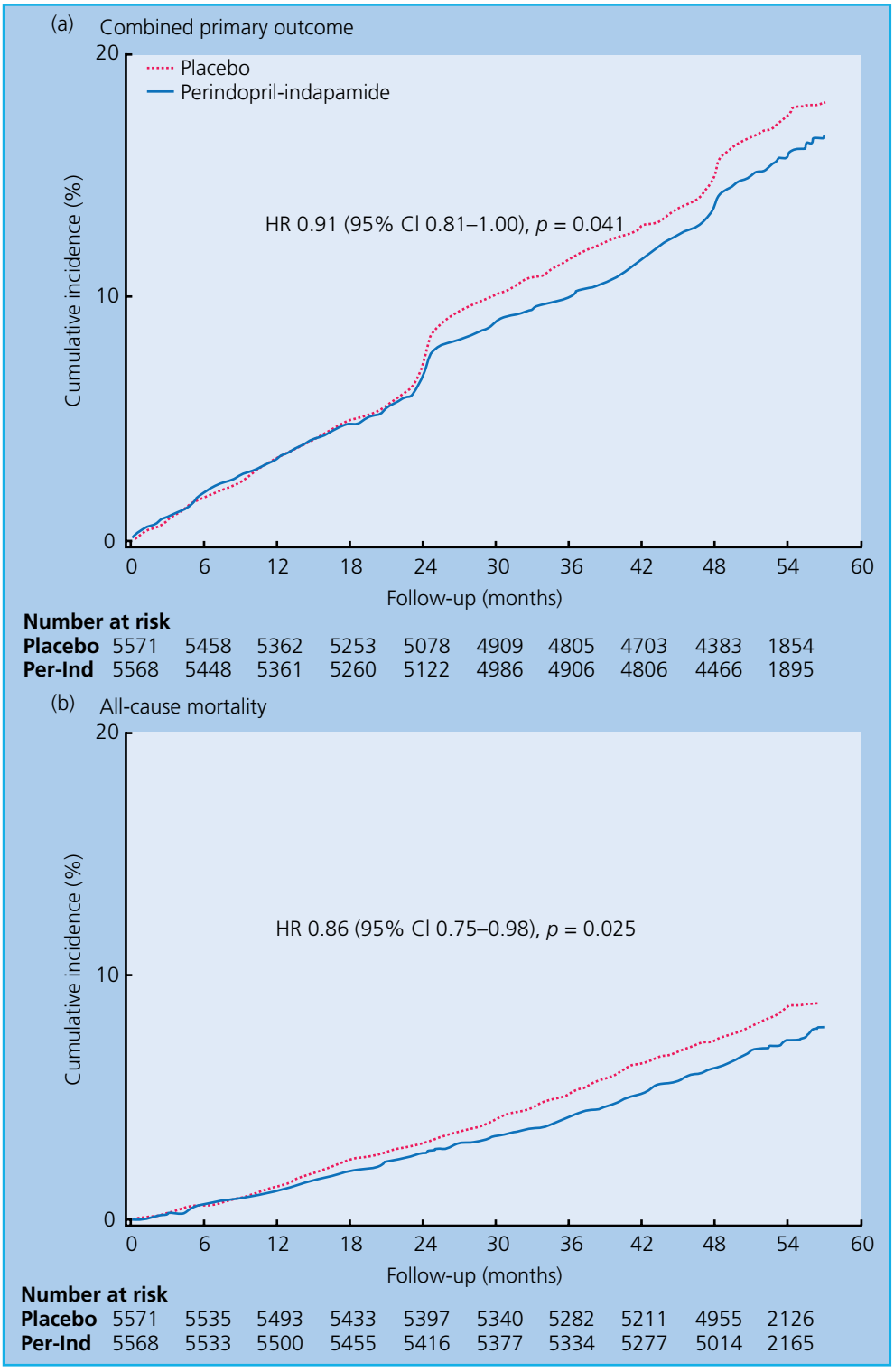

Figure 47.7 Kaplan–Meier curves for the (a) primary outcome and (b) all-cause mortality in the two study groups in the ADVANCE Trial [86]. The combined primary outcome was a composite of major macrovascular and microvascular events. Major macrovascular events were cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Major microvascular events were new or worsening nephropathy or retinopathy. CI, confidence interval; HR, hazard ratio.

but within the systolic blood pressure range of 130–140 mmHg for older people, if tolerated.

Finally, it takes a multifactorial approach to address and to treat all major cardiovascular risk factors, not only blood pressure, to achieve lasting cardiovascular protection in persons with type 2 diabetes, as evidenced by the Steno-2 trial [103]. This strategy was also cost-effective [104] and should therefore be widely implemented.

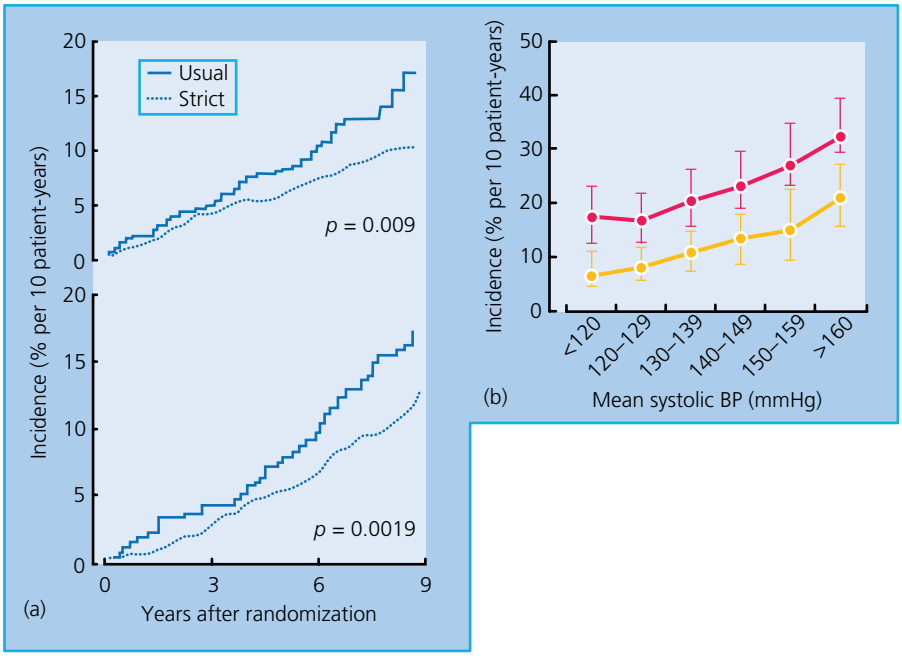

Figure 47.8 Treating hypertension improves the prognosis in type 2 diabetes. (a) Stricter blood pressure (BP) control (mean pressure 144/82 mmHg) significantly reduced the risks of both microvascular complications (top) and diabetes-related death (bottom), compared with less strict control (mean 154/82 mmHg). (b) Relationship between blood pressure and rates of microvascular disease and myocardial infarction. Lowering the blood pressure progressively reduced the risk of microvascular complications, but there was no significant effect on myocardial. The red line represents myocardial infarction and the yellow line represents microvascular complications. Source: UKPDS 1998 [5]. Reproduced with permission from BMJ Publishing Group Ltd.

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48 Dyslipidaemia and Diabetes

Adie Viljoen[1,2], Ahmed Handhle[1,2], and Anthony S. Wierzbicki[3]

[1] East Hertfordshire Hospitals Trust, Lister Hospital, Stevenage, UK
[2] Department of Clinical Biochemistry, Addenbrooke's Hospital, Cambridge, UK
[3] Guy's & St Thomas Hospitals, London, UK

Key points

- The greatest long-term risk in diabetes is cardiovascular disease, with macrovascular disease being the cause of 80% of mortality.
- Epidemiological studies have established that hyperglycaemia, nephropathy, and dyslipidaemia are risk factors for cardiovascular disease in type 1 diabetes.
- Low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, smoking, and hypertension are the principal risk factors in type 2 diabetes.
- In type 2 diabetes optimized glycaemic management has modest effects in reducing cardiovascular disease endpoints.
- The dyslipidaemia of type 2 diabetes is associated with elevated triglycerides, reduced HDL cholesterol, and small dense particles.
- Reduction of LDL cholesterol with statins has consistently shown cardiovascular event reductions of ~21% per 1 mmol/l LDL cholesterol.
- Monotherapy with fibrates led to a modest reduction in events in people with type 2 diabetes in the FIELD study.
- Trials now underway will allow the efficacy of combination lipid-lowering therapies in diabetes to be determined.
- Optimal management of all risk factors can reduce cardiovascular events and mortality in diabetes by 50%.

An association between diabetes and heart disease was described more than a century ago. In 1906, it was hypothesized that this association was due to atherosclerosis. The importance of diabetes as a cardiovascular disease (CVD) risk factor became established following the Framingham Study and this was subsequently confirmed by other landmark studies [1, 2]. The magnitude of diabetes as a CVD risk factor is substantial, with the increase in cardiovascular risk being two- to fourfold. Many guidelines regard diabetes as a coronary heart disease (CHD) risk equivalent [3, 4]. This concept is based originally on a Finnish cohort, which showed comparable risk of CHD outcomes such as myocardial infarction (MI) and CHD death, between individuals with type 2 diabetes for >10 years and people with established CHD [5]. This was still apparent after adjusting for known risk factors such as age, sex, hypertension, total cholesterol, and smoking. The Organization to Assess Strategies for Ischemic Syndromes (OASIS) study showed that people with diabetes and with no previous CVD have the same long-term morbidity and mortality as normoglycaemic individuals with established CVD after hospitalization for unstable coronary artery disease (CAD) [6]. However, there is wide variation in the rate of CHD in diabetes, which depends on the population studied, duration of diabetes, as well as existing risk factors (Figure 48.1) [7, 8]. This equivalence has not been confirmed by subsequent studies and it also seems less valid in older individuals, where those with existing CHD have a greater risk than people with diabetes without CHD [8–10]. People with type 1 diabetes are also at increased risk for CVD [11, 12]. Although people with type 1 diabetes mostly present at an earlier age, the rates of CVD are increased at all ages [13]. Concomitant CVD risk factors also differ according to the type of diabetes. Other markers of CVD risk in people with diabetes include diabetic retinopathy, autonomic neuropathy, erectile dysfunction, microalbuminuria, and proteinuria [14], with nephropathy being the most significant. In type 1 diabetes the risk of premature CVD is increased 7-fold for mortality and 12-fold for CVD events with sub-optimal risk factor management, and 1.3-fold for mortality and 1.8-fold for MI with optimal management [10].

In general, people with diabetes have a 2–4-fold increased CVD risk compared with people without diabetes [15, 16]. Most guidelines do not recommend formal CVD risk estimation in diabetes due to the significant risk these individuals already have and the tendency of risk calculation equations to underestimate risk in this group. Clinicians, however, may still opt to estimate the risk by employing various validated risk calculators, which include QRISK specific diabetes scores in the UK [17]. These predict risk with variable accuracy [18] and may depend on interpolated data [19]. As all methods of CVD risk estimation suffer from distinct limitations, so clinical judgement remains necessary to accurately risk stratify and select and titrate the appropriate treatment.

Cardiovascular disease risk factors in diabetes

Glucose

A risk continuum exists across a broad glucose concentration range, which incorporates individuals without diabetes, with the risk of CVD being lowest when the fasting blood glucose is between

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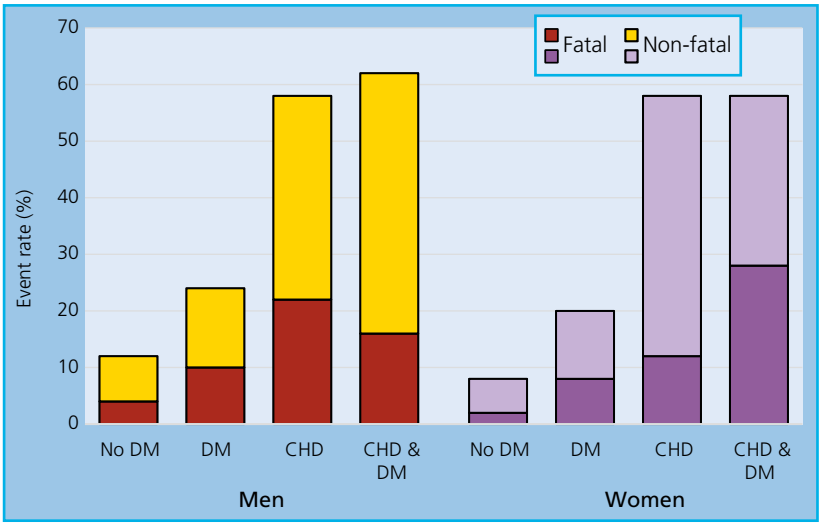

Figure 48.1 Lack of equivalence of cardiovascular risk in individuals with previous coronary heart disease (CHD) and those with diabetes (DM). Source: Data from Howard et al. 2006 [7].

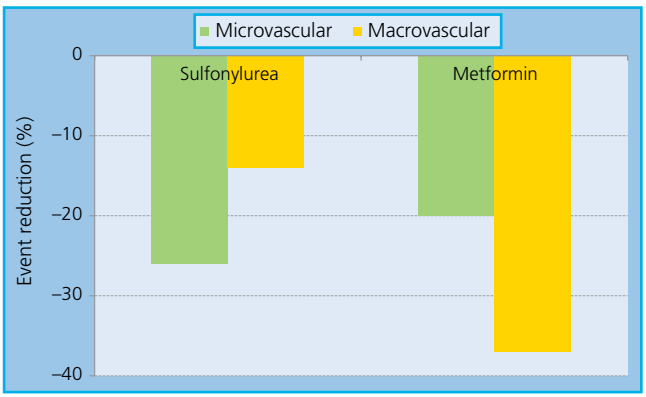

Figure 48.2 Results of the UK Prospective Diabetes Study for microvascular and macrovascular events at 10-year follow-up. Source: Data from Holman et al. 2008 [24].

4 and 4.9 mmol/l [20–22]. Epidemiological studies show a consistent association between blood glucose and atherosclerosis, but only recently have intervention studies shown an improvement in CVD outcomes by reducing glucose [16]. In the Epidemiology of Diabetes Interventions and Complications (EDIC) [23] follow-up from the Diabetes Control and Complications Trial (DCCT), glucose lowering in people with type 1 diabetes was associated with a long-term benefit with regard to CVD complications that became apparent only years after recruitment. In type 2 diabetes, 10 year follow-up data from the UK Prospective Diabetes Study (UKPDS) intensive glucose therapy showed long-term beneficial effects on macrovascular outcomes [24]. However, unlike the microvascular benefits, risk reductions for MI and death from any cause were observed only with extended post-trial follow-up (Figure 48.2). These results suggested that improved glucose management may result in a larger CVD risk reduction in persons with type 1 diabetes than among those with type 2 diabetes, which is consistent with the results of one meta-analysis (Figure 48.3).

Dyslipidaemia

The reasons for the excess risk for CVD in diabetes are numerous and varied and in part relate to the lipid abnormalities seen in diabetes [25–27]. Enhanced glycation of lipoproteins has direct effects on lipoprotein metabolism, as these glycated lipoproteins are handled differently by lipoprotein receptors, particularly of the scavenger group, thus promoting atherogenesis [27, 28]. Enhanced glycation also amplifies the effects of oxidative stress on lipoproteins and this therefore implicates both type 1 diabetes and type 2 diabetes [29]. Diabetic dyslipidaemia refers to the atherogenic lipid abnormalities typically seen in persons with type 2 diabetes, characterized by elevated triglyceride (TG)-rich remnant lipoproteins (routinely measured as excess TG), small dense low-density lipoprotein particles (sdLDL) and low high-density lipoprotein (HDL) cholesterol concentrations [30, 31].

Several factors are likely to be responsible for diabetic dyslipidaemia, including:

- Insulin effects on liver apolipoprotein production.
- Downregulation of lipoprotein lipase (LPL) as opposed to hepatic lipase (HL).
- Increased cholesteryl ester transfer protein (CETP) activity.
- Peripheral actions of insulin on adipose and muscle [27].

Targeting dyslipidaemia has proven effective in preventing the macrovascular complications of diabetes. For many years the benefits of intervention on lipoproteins as CVD risk factors in diabetes were uncertain, as people with diabetes were excluded from trials of lipid-lowering therapies. No pre-specified data exist from early studies with bile acid sequestrants, fibrates, or nicotinic acid, but later studies with statins and fibrates have been performed in people with type 2 diabetes. Evidence has accumulated for LDL cholesterol being the prime risk factor for atherosclerosis [32], but more recently increased recognition of the role of TG-rich lipoproteins in CVD [33] has led to the suggestion that non-HDL cholesterol (difference of total and HDL cholesterol) might be a better guide to CVD risk, especially in diabetes [34].

Low-density lipoprotein cholesterol

LDL cholesterol is identified as the primary target of lipid-lowering therapy. Most laboratories report a calculated LDL cholesterol using the Friedewald equation, which tends to underestimate LDL cholesterol compared to direct assays or newer equations, especially if TGs are increased, as is often the case in people with diabetes [35]. Epidemiological studies show a strong association of cholesterol fractions including total cholesterol, LDL cholesterol, and non-HDL cholesterol (a measure of apolipoprotein B_{100} containing particles

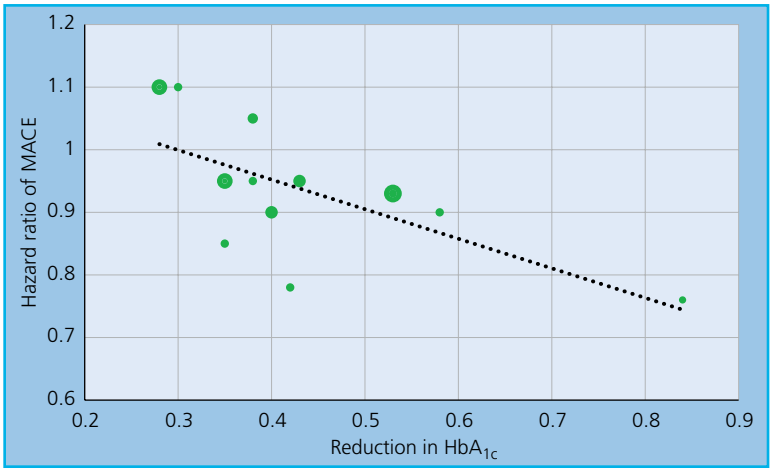

Figure 48.3 Meta-regression of improved glycated haemoglobin (HbA_{1c}) and cardiovascular events. MACE, major adverse cardiovascular events. Source: Data from Giugliano et al. 2019 [85].

including TG-rich lipoproteins) with CVD in people with and without diabetes [32, 34, 36]. Analysis of the UKPDS showed that LDL cholesterol was the strongest risk factor for CHD in the study population and HDL cholesterol was the second strongest [37]. In contrast, in type 1 diabetes the EDIC-DCCT collaboration shows stronger relationships for glycaemic and blood pressure management compared to lipids for CVD risk [38], but as participants age then LDL cholesterol becomes more significant [39].

Low-density lipoprotein subfractions

The LDL class comprises a heterogeneous population of particles with respect to lipid composition, charge, density, and particle size and shape [40]. The sizes of LDL particles fall between the large TG-enriched VLDL and the dense and small protein-rich HDL. In addition, these small dense LDL (sdLDL) particles are more atherogenic as they are more readily oxidized and glycated [30, 41]. Oxidized LDL delivers cholesterol to the atherosclerotic plaque in an unregulated way through uptake by the macrophage and is increased in diabetes [42]. New automated assays are now available for sdLDL [43] and may be more practical than magnetic resonance or gel assays, though some standardization is still required [44].

Large numbers of studies have confirmed the association of sdLDL with CVD [45]. However, no prospective studies have specifically examined whether altering particle size profiles results in benefits on CVD events, though analysis of the Veterans Affairs HDL Intervention Trial (VA-HIT) fibrate study does suggest some role for this mechanism [46]. Even with effective LDL cholesterol treatment, the residual risk of further CVD events remains high, emphasizing the importance of improving other abnormalities and other CVD risk factors commonly observed in these individuals [47, 48].

Triglycerides

The reason for the elevated TGs in diabetes is complex. However, it is also because of this derangement that it has been suggested that diabetes should not be called mellitus but rather 'lipidus' [49]. Defects in insulin action and hyperglycaemia can lead to changes in plasma lipoproteins in persons with diabetes. Alternatively, especially in the case of type 2 diabetes, the obesity/insulin-resistant metabolic disarray that is at the root of this form of diabetes could itself lead to lipid abnormalities exclusive of hyperglycaemia [27]. It is this molecular interplay between lipid and carbohydrate metabolism that has led to what might be termed a 'lipocentric' view of the pathogenesis of insulin resistance and type 2 diabetes [50]. As fatty acids play such a central role in insulin sensitivity, obesity, and type 2 diabetes, it follows that the major disturbance in lipoprotein metabolism in diabetes is found in the TG-rich lipoproteins, stemming from abnormalities in chylomicron synthesis and clearance [51].

Triglycerides (also referred to as triacylglycerol) are formed from a single molecule of glycerol combined with three fatty acids and represent a heterogeneous group of molecules that, most frequently are measured collectively, as a 'family' of analytes [52]. As high serum TG levels are associated with abnormal lipoprotein metabolism, as well as with other cardiovascular risk factors including obesity, insulin resistance, diabetes, and low levels of HDL cholesterol, it is difficult to distinguish between cause and effect and to establish TGs as an independent CVD risk factor. However, meta-analyses show that elevated serum TG levels are associated with increased risk for atherosclerotic events in epidemiological cohort studies [33], but some familial causes of hypertriglyceridaemia have no apparent effect on atherosclerotic vascular disease [53].

The two main sources of plasma TGs are exogenous (i.e. from dietary fat) carried in chylomicrons (CM), and endogenous (from the liver) and carried in VLDL particles. In capillaries within fat and muscle tissue, these lipoproteins and chylomicrons are hydrolysed by LPL into free fatty acids. LPL is activated by apolipoprotein C-II (apoC-II), cleaving the TG core and releasing free fatty acids, which can be oxidized by muscle for energy or kept in adipose tissue for future use, and inhibited by the action of apoC-III [54]. In routine clinical practice hypertriglyceridaemia is the most frequent lipoprotein abnormality found in dysregulated diabetes. The mechanisms for these include increased absorption and production of TGs, allied with reduced catabolism of TG-rich particles caused by decreased activity of LPL. Increased adipose tissue lipolysis is a consequence of insulin resistance and/or insulin deficiency. The increased lipolysis results in increased fatty acid release from fat cells, with increase in fatty acid transport to the liver. Studies in tissue cultures, animal experiments [55], and in humans [56] suggest that fatty acids modulate liver apoB secretion. In parallel with increased liver TGs, production of apoB (the major protein component of VLDL and LDL) and hence the number of

particles are increased in type 2 diabetes. Microsomal triglyceride transfer protein (MTP) assembles the chylomicron in the intestine and the VLDL particle in the liver. MTP has been shown to be increased in the intestine of people with diabetes [57]. Cholesterol absorption also seems to be adversely influenced in people with diabetes. Levels of NPC1L1 protein, which plays a critical role in the absorption of cholesterol, are increased in diabetes. The ATP-binding cassette transporters ABC-G5 and ABC-G8 dimerize to form a functional complex necessary for efflux of dietary cholesterol and non-cholesterol sterols from the intestine and liver. These proteins have been shown to be reduced in diabetes in both liver and intestine. LPL is an insulin-dependent enzyme that is responsible for the conversion of lipoprotein TG into free fatty acids and has several other activities relating to lipid and carbohydrate metabolism [58]. Both in type 1 diabetes and type 2 diabetes, there is an associated reduced LPL activity, which is further suppressed by adipose-derived cytokines such as tumour necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) [27].

Statins form the mainstay of lipid management based on their efficacy in lowering LDL cholesterol, but their effects on components of the atherogenic dyslipidaemia associated with type 2 diabetes are more modest, reducing TGs at most by 15–30% and raising HDL cholesterol typically by less than 10% [59]. Interventions usually affect both TGs and other lipid fractions and so it is difficult to distinguish between the individual benefits, but a residual benefit of 9% per 1 mmol/l reduction in TGs exists even after excluding the TG-reducing effects of omega-3 fatty acids [60].

High-density lipoprotein cholesterol

Like LDL, HDL also comprises a heterogeneous population of particles. The inverse relationship between HDL cholesterol levels and atherosclerotic CVD provides the epidemiological basis for the widely accepted hypothesis that HDL is atheroprotective [34]. HDL has several distinct but potentially overlapping atheroprotective functions [61, 62]. These include the well-known action on reverse cholesterol transport [63] as well as reductions in oxidative stress and innate immunity and inflammation [64]. More HDL-associated proteins are involved in immune and inflammatory functions than in lipid transport and metabolism, suggesting the fundamental role for HDL in innate immunity [65, 66]. There are several reasons that could account for the decrease in HDL cholesterol in diabetes [27]. The CETP-mediated exchange of VLDL TG for HDL cholesteryl esters is accelerated in the presence of hypertriglyceridaemia [67]. The TG in HDL is a substrate for plasma lipases, especially hepatic lipase that converts HDL to a smaller particle that is more rapidly cleared from the plasma. Precursors of advanced glycation end-products can also impair reverse cholesterol transport by HDL.

Treatment options

Dietary treatments

Though many studies exist of different diets in people with diabetes, they typically only report short-term changes in lipids. Cardiovascular outcome studies are rarer and generally underpowered, but meta-analyses suggest a benefit for Mediterranean diets in populations at risk of CVD [68–70]. Recently, the Prevención con Dieta Mediterránea (PREDIMED) trial in 7447 people at high CVD risk, including 50% with type 2 diabetes, showed a 28–31% reduction in CVD events with a Mediterranean diet enriched in nuts or olive oil compared with a control diet, but was likely underpowered for this subgroup [71]. Trials involving weight loss improve lipids by reducing hepatic steatosis (fatty liver) and allied secondary features such as the production of TG-rich lipoproteins. The Look AHEAD (Action for Health in Diabetes) study randomized 5145 obese people with type 2 diabetes to intensive lifestyle intervention or diabetes support and education for 9.6 years [72]. It showed no significant difference in CVD outcomes or safety despite improvements in surrogate and secondary outcomes such as glucose, lipids, blood pressure, sleep apnoea, liver fat, kidney disease, or retinopathy allied with a reduced need for diabetes medications.

Statins

Statins (2-hydroxy-methyl-glutaryl coenzyme A reductase inhibitors) work by inhibiting the rate-limiting step in cholesterol synthesis [67]. This results in intracellular depletion of cholesterol in hepatocytes that is sensed in the endoplasmic reticulum and results in cleavage of the sensor protein-releasing sterol receptor element–binding protein-2 (SREBP-2), which upregulates nuclear synthesis of cholesterol synthetic enzymes and the LDL receptor [67]. Increased LDL receptor expression causes a reduction in plasma cholesterol. Statins deliver a 20–50% reduction in LDL cholesterol, but 1% of people taking the drug develop myalgia with these agents. Even relatively modern studies discouraged recruitment or restricted entry to people with hypercholesterolaemia and reasonable levels of glycaemia (glycated haemoglobin [HbA_{1c}] <64 mmol/nmol; 8%), as in the Scandinavian Simvastatin Survival Study (4S), the first major statin trial [73]. The 4S included only 202 people with type 2 diabetes in 4444 participants. However, in this small group of participants, simvastatin therapy was associated with a 55% reduction in major CHD (fatal and non-fatal CHD; $p = 0.002$) compared with a 32% reduction in major CHD in people without diabetes [74]. The absolute benefit of cholesterol lowering in type 2 diabetes was greater than that in people with CHD but without diabetes, because persons with type 2 diabetes had a higher absolute risk of atherosclerotic events and CHD. This notion was later confirmed in studies that also recruited a subgroup of individuals with diabetes [75].

The Collaborative Atorvastatin Diabetes Study (CARDS) [76] and the Heart Protection Study (HPS) [77] included people with type 2 diabetes randomized in a double-blind, placebo-controlled design to atorvastatin 10 mg/d in CARDS and to simvastatin 40 mg/d in HPS. This produced, respectively, a 40% and 33% reduction in LDL cholesterol associated with a 37% and 31% reduction in combined CVD endpoints. While HPS was mostly a secondary prevention study recruiting people with established CVD, it included a pre-specified subgroup of 5963 individuals with diabetes (29% of the total study group) [77] of whom 600 persons had type 1 diabetes. The CARDS trial solely included individuals with type 2 diabetes and with more than one other risk factor (e.g. uncontrolled hypertension and/or microalbuminuria) but without prior overt CVD. The study was terminated two years early after showing early benefits. The data from trials and subgroups with diabetes were integrated in an individual patient-level meta-analysis of 18 686 individuals (type 1 diabetes 1466; type 2 diabetes 17 220), which showed that over 4.3 years of follow-up and 3247 major vascular events statin therapy reduced mortality by 9% per 1 mmol LDL cholesterol similar to the 13% per 1 mmol/l LDL cholesterol in the group without diabetes, driven by a 13% per 1 mmol/l LDL cholesterol reduction in CVD

death. Overall a 21% per 1 mmol/L LDL cholesterol reduction was seen in total vascular events, similar to the groups without diabetes in the studies [78].

Studies have investigated individuals with diabetes and nephropathy. In Die Deutsche Dialyse Diabetes (4D) study in persons with end-stage renal disease on dialysis with type 2 diabetes, aggressive LDL cholesterol reduction reduced events by a non-significant 8%, despite a 41% reduction in LDL cholesterol [79]. The Simvastatin Heart and Renal Protection (SHARP) study in 9270 individuals with chronic kidney disease (CKD stages 3–5), which included a subgroup with type 2 diabetes (n = 2094), simvastatin 20 mg, and added ezetimibe 10 mg, showed a similar 22% reduction in CVD events to 14% in the normoglycaemic group, with the greatest relative benefits with lower severity of CKD [80].

Cholesterol absorption and resorption inhibitors

Bile acid sequestrants are one of the oldest lipid-lowering therapies. They inhibit resorption–absorption of cholesterol in the terminal ileum. Data in people with diabetes are limited to their effects on lipids, where they reduce LDL cholesterol by 20% but tend to increase TGs, despite having a small effect on improving glucose levels. They have a poor side-effect profile with high rates of gastrointestinal disturbance. There are no CVD outcome studies with these drugs that have recruited any people with diabetes, so their effects on hard outcomes are unknown.

The cholesterol absorption inhibitor ezetimibe works by reducing the upper intestinal cholesterol absorption by inhibiting the function of Niemann-Pick C1-like protein 1 (NPC1L1) transporter to produce a 21% reduction in LDL cholesterol and, in contrast to bile acid sequestrants, has little effect on other lipid fractions. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study compared the addition of ezetimibe with placebo in 18 144 individuals with acute coronary syndromes (ACS) optimized on statin therapy [81]. Statin optimization reduced LDL cholesterol from 2.4 to 1.8 mmol/l and ezetimibe delivered a further 0.4 mmol/l reduction. The 4933 persons with type 2 diabetes showed a greater 14% reduction in CVD events compared with 3% in the group without diabetes (p = 0.02). They had double the CVD event rate and thus half the number needed to treat (NNT) of 12, as opposed to 25 for CVD events including procedures in the overall study.

Proprotein convertase subtilisin kexin-9 inhibitors

Proprotein convertase subtilisin kexin-9 (PCSK9) inhibitors act to reduce LDL cholesterol by upregulating LDL receptor function and reduce LDL cholesterol by 57% [82]. The most recent trials in individuals with ACS have used PCSK9 inhibitors and required the presence of additional CVD risk factors, including type 2 diabetes. All individuals were optimized on statin therapy, but ezetimibe use was low (<5%). In the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) study, after 2–3 years CVD events were reduced by 16% after one year, rising to 25% after two years overall, in line with the 1 mmol/l reduction in LDL cholesterol after allowance was made for initiation effects in a secondary prevention population [83]. Effects in individuals with diabetes were similar to those without [84].

The accumulated evidence strongly supports the efficacy of LDL cholesterol–lowering therapies in reducing CVD, with the latest regression analyses suggesting benefits of 17% event reduction per 1 mmol/l LDL cholesterol reduction for all LDL cholesterol therapies, with no difference in results seen in individuals with diabetes (Figure 48.4) [86]. However, some therapies reducing TGs cause an increase in measured LDL cholesterol, mostly through enhanced conversion of very low-density lipoprotein (VLDL) to LDL particles, with the effects being proportional to baseline TGs. For instance, omega-3 fatty acids raise LDL cholesterol by 6% [87], while sodium–glucose cotransporter 2 (SGLT-2) inhibitors raise LDL cholesterol by 0.1 mmol/l (3%) and non-HDL cholesterol by 0.09 mmol/l (2%) [88]. The relevance of these secondary rises in LDL cholesterol is unclear, as these therapies show lipid-independent effects on rates of CVD.

Fibrates

The 'fibrate' class of lipid-lowering drugs is useful for lowering elevated TG or non-HDL cholesterol levels, as these agents, which act on peroxisomal proliferator-activating receptor alpha (PPAR-α), increase lipoprotein lipase activity, reduce apoC-III, and may increase HDL cholesterol or decrease fibrinogen [89]. VA-HIT evaluated the potential benefits of gemfibrozil in 2531 men who had suffered an acute MI. Individuals with relatively low LDL cholesterol (<3.6 mmol/l) and low HDL cholesterol (<1.0 mmol/l) were recruited. The primary CVD endpoint of fatal and non-fatal MI was reduced by 22% [90]. Similar effects were seen in the 25% of

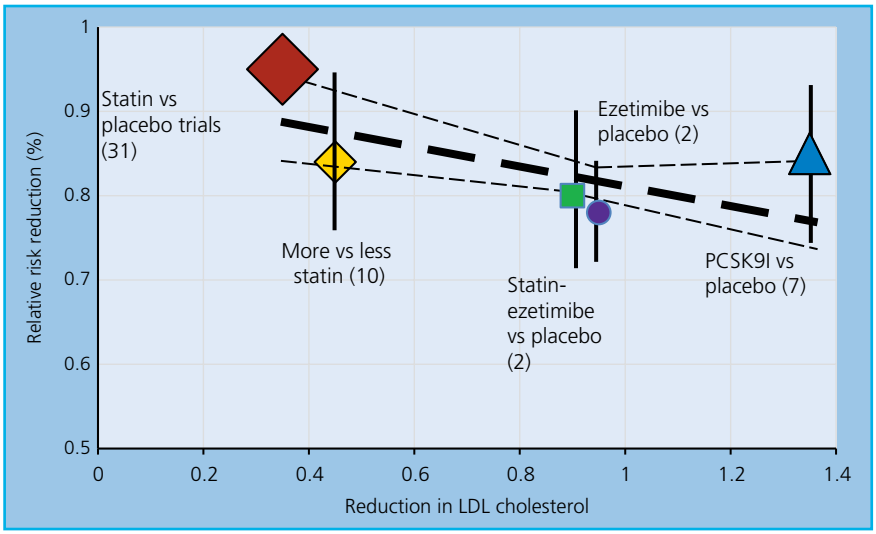

Figure 48.4 Meta-regression of effects of low-density lipoprotein (LDL) cholesterol-lowering therapies on cardiovascular event rates. PCSK9i, proprotein convertase subtilisin kexin-9 inhibitor. Source: Data from Wang et al. 2020 [86].

participants with type 2 diabetes. These outcomes were achieved despite relatively small changes in HDL cholesterol (8%) and no change in LDL cholesterol (0%). An exploration of the effect of gemfibrozil showed that the principal effect of the fibrate treatment was a 31% reduction in TGs, which reflects changes in particle sizes, but this effect was not related to CVD event reduction [91]. The subgroup of individuals with type 2 diabetes showed a relative risk reduction of 32% compared to 18% in the group without diabetes [92].

However, later fibrate trials showed less benefit. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study randomized 9795 individuals with type 2 diabetes to fenofibrate (200 mg daily) or placebo who were not on statin treatment at the beginning of the study and participants were treated for five years [93]. A non-significant 11% reduction in the primary endpoint of CHD was found, but a reduction in the secondary endpoint of total CVD events was achieved (p = 0.035). The study was confounded by asymmetrical statin drop-in, with many more individuals with diabetes in the placebo arm being initiated on statin therapy during the trial (17%) than those in the fenofibrate arm (8%) [44]. As statin therapy is core to lipid management, the question arose as to whether fibrates added anything to statin therapy. *Post hoc* analyses suggested benefits in individuals with atherogenic lipid profiles (high TG, low HDL cholesterol).

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study randomized 5518 individuals with type 2 diabetes and 37% with CVD to fenofibrate 200 mg on top of statin therapy [94]. There were no specific HDL cholesterol or TG recruitment criteria. After five years fibrate therapy delivered a 9% non-significant reduction in CVD events. The pre-specified dyslipidaemic subgroup (n = 931) showed a 29% reduction in CVD events compared to no change in the non-dyslipidaemic group (p = 0.06). The overall results led to fibrates being discouraged in use in combination therapy in the USA. As the role of fibrates added to statins in dyslipidaemic individuals with type 2 diabetes remains unclear, a further trial (Pemafibrate to Reduce cardiovascular OutcoMes by reducing triglycerides IN patiENts with diabeTes, PROMINENT) is now underway using the selective PPAR modulator (SPARM) pemafibrate, which has similar lipid effects to fibrates [95]. Lipid-lowering fibrate therapy in both the FIELD and ACCORD studies was associated with benefits on microvascular disease such as retinopathy and nephropathy [96].

It is difficult to compare fibrate trials as they seem to give heterogeneous results depending on the compound used. No fibrate trials have shown a reduction in all-cause mortality, but meta-analyses suggest they may reduce non-fatal MI (Figure 48.5), although some of this can be explained by their predicted reduction in LDL cholesterol [97, 98]. However, this does not explain the effects seen with gemfibrozil, which does not reduce LDL cholesterol.

Niacin

Nicotinic acid (niacin) reduces hypertriglyceridaemia and LDL cholesterol and raises HDL cholesterol, so it has been referred to as the 'broad-spectrum' lipid drug [99]. Niacin was the first lipid-lowering agent to show a significant reduction in CVD events but not mortality. The Coronary Drug Project (CDP) randomized 3908 men with previous MI to either niacin or placebo and showed reduced CVD events but not mortality [100]. In the 15-year post-trial follow-up, niacin was associated with 11% lower mortality [101]. Unfortunately, niacin has been hampered by its side effects, particularly flushing (though amelioration strategies exist) [102] and hyperglycaemia. Niacin adversely affects glucose levels in a dose-related manner [103] and wider variations are seen in practice [104], but it was as effective at lowering CVD outcomes in individuals with hyperglycaemia as in persons with normoglycaemia in the CDP [105]. The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: Impact on Global Health outcomes (AIM-HIGH) recruited 3414 individuals with CVD and low HDL cholesterol [106]. It used extended-release niacin on top of optimized statin therapy and showed no benefit on CVD events overall or in any subgroup. Similarly, the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) recruited 25 673 individuals with CVD or at high risk of CVD, including 8299 persons with diabetes, but showed no benefits on CVD outcomes and an excess of infection or thrombocytopaenia with niacin therapy. As in AIM-HIGH, all participants were optimized on statin therapy, but HPS-THRIVE differed in lacking pre-specified lipid recruitment criteria (raised TG-to-HDL cholesterol atherogenic index) and in using extended-release niacin allied with laropiprant (an inhibitor of prostaglandin receptor D1, which reduces the flushing) [107]. These two trials have downgraded the usefulness of niacin in CVD.

Omega-3 fatty acids

Omega-3 fatty acids have complex actions, including effects on inflammation and a dose-dependent reduction in TGs mediated through the free fatty acid receptor 4 (FFAR-4) [108]. The efficacy

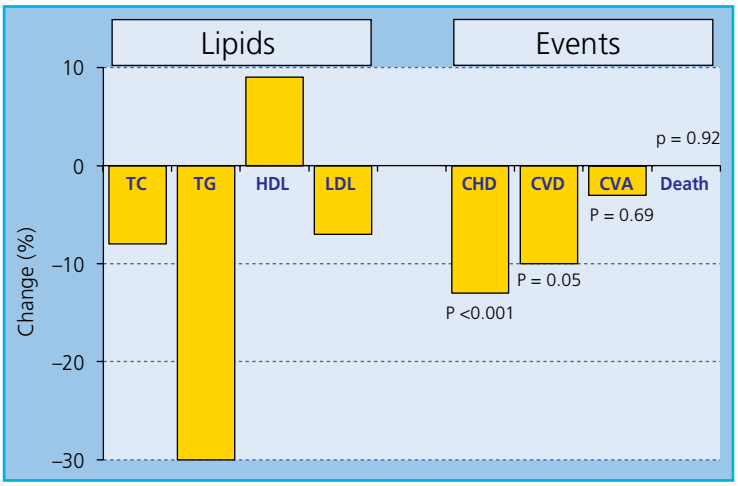

Figure 48.5 Fibrates: meta-analyses of effects on lipids and cardiovascular events. CHD, coronary heart disease; CVA, stroke–cerebrovascular accident; CVD, cardiovascular disease; HDH, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides. Source: Data from Saha et al. 2007 [97] (10 studies, n = 36 489) and Jun et al. 2010 [98] (18 studies, n = 45 058).

of omega-3 fatty acids in reducing TGs was validated in the MARINE trial, which recruited individuals with significant hypertriglyceridaemia (TG >4.5 mmol/l) [109]. The role of omega-3 fatty acids in CVD and type 2 diabetes is complicated. Early trials of dietary supplementation and later pharmacological preparations (e.g. docosahexanenoic acid [DHA]/eicosapentanenoic acid [EPA]) showed benefits. Later, their effects were investigated in people with impaired glycaemia or type 2 diabetes in the Outcome Reduction with Initial Glargine Intervention (ORIGIN) study [110] and then in individuals with type 2 diabetes in the A Study of Cardiovascular Events iN Diabetes (ASCEND) trials [111] and showed no benefit. When data are meta-analysed, there is no benefit to omega-3 fatty acid therapy at a low dose (<1 g) on CVD events (Figure 48.6) [112]. However, a trial in this meta-analysis that used higher doses of omega-3 fatty acids showed different results, suggesting that some heterogeneity was present. In the Japan EPA Lipid Intervention Study (JELIS), 18 645 individuals with CVD including 16% with type 2 diabetes were randomized to 2 g EPA on top of a fish-rich diet [113]. Added EPA therapy reduced CVD events by 19% in all participants and a similar 14% in the type 2 diabetes subgroup, independent of any effects of lipids. The effect of 4 g of an EPA derivative compared with mineral oil was investigated in 8179 individuals in the Reduction of Cardiovascular Events with Icosapent Ethyl Intervention Trial (REDUCE-IT) study [114] in individuals with CVD optimized on statin therapy and with TG >2.3 mmol/l (later >1.7 mmol/l). Treatment was associated with a 25% CVD benefit independent of lipids in the overall study and 23% in the 4787 (58%) individuals with type 2 diabetes. The long-term outcomes study, the STatin Residual risk with Epanova iN hiGh cardiovascular risk patienTs with Hypertriglyceridemia (STRENGTH) trial, recruited 13 708 participants of whom 9170 had diabetes with an additional risk factor as well as dyslipidaemia with average TG 2.7 mmol/l and HDL cholesterol 0.93 mmol/l, and compared 2 g EPA-2g DHA with corn oil [115]. EPA-DHA reduced TG by 19%, non-HDL cholesterol by 6%, and C-reactive protein by 14%, but raised LDL cholesterol by 2.3%. It had no effect in reducing CVD events. Furthermore, EPA therapy was associated with a 69% increase in new atrial fibrillation and gastrointestinal side effects. Some but not all high-dose studies with EPA showed CVD benefits and so there may be a role for EPA in people with dyslipidaemia and optimal LDL cholesterol, but there is no role for low-dose therapies.

Other triglyceride-reducing agents

Anti-diabetes agents may also influence TG concentrations due to the peripheral actions of insulin on adipose and muscle or via their action on LPL. In poorly managed type 1 diabetes and even ketoacidosis, hypertriglyceridaemia and reduced HDL cholesterol are seen to occur, and these are most often corrected with insulin therapy. In type 2 diabetes, metformin [116], sulfonylureas [117], and acarbose [118] all show modest reductions in TG that correlate with HbA_{1c} [119, 120]. In general, thiazolidinediones have better overall effects on lipids compared to sulfonylureas or insulin [121]. However, pioglitazone and rosiglitazone have distinctly different effects on the lipid profile [89, 122]. Pioglitazone is associated with a reduction in TG, rosiglitazone with increased concentrations. In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROACTIVE) study, pioglitazone added to other anti-diabetes therapies in individuals with type 2 diabetes reduced CVD events by 11% in the main secondary endpoint [123].

Several other interventions exist that reduce TG secondary to their action in reducing weight [124]. Orlistat has been shown to prevent progression to diabetes in the XENical in the prevention of Diabetes in Obese Subjects (XENDOS) study [125]. Similar effects are seen with glucagon-like protein-1 (GLP-1) receptor agonists such as semaglutide, which can reduce body weight by up to 10 kg [126].

Agents to increase high-density lipoprotein cholesterol

As opposed to LDL cholesterol lowering, therapies for intervening in order to raise HDL cholesterol have proven to be not that simple. Some HDL therapies may reduce CVD without changing HDL cholesterol concentrations. A preliminary intravascular ultrasound study (IVUS) of a hyperfunctional form of apoA-1 ($apoA\text{-}1_{Milano}$) showed regression of coronary atherosclerosis [127], but a later larger study showed no benefits although, unusually, regression was seen in the placebo group [128]. CETP inhibitors raise plasma HDL

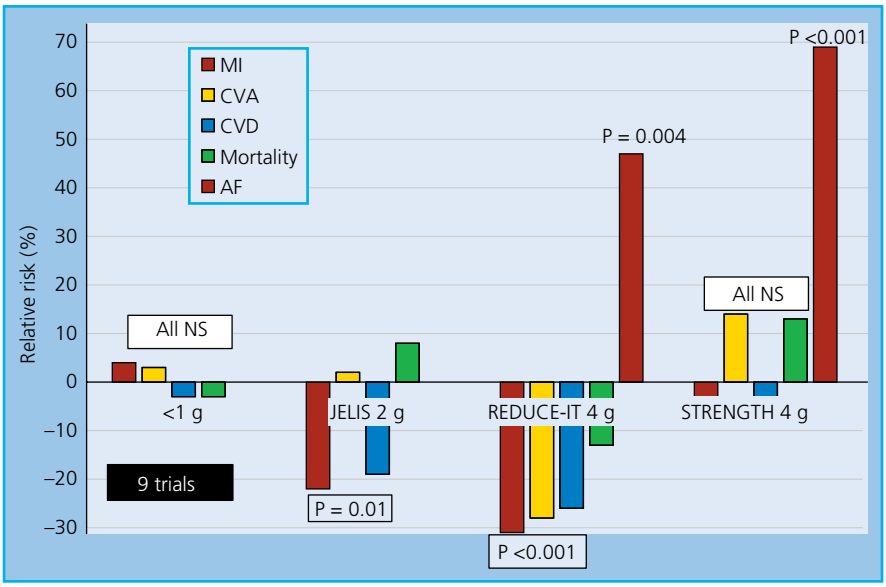

Figure 48.6 Effects of omega-3 fatty acid preparations on cardiovascular events and new-onset atrial fibrillation. AF, atrial fibrillation; CVA, stroke–cerebrovascular accident; CVD, cardiovascular disease; MI, myocardial infarction; NS, non-significant. Source: Data from Aung et al. 2018 [112].

cholesterol and reduce LDL cholesterol, but have lesser effects on HDL cholesterol turnover. Torcetrapib, the first CETP inhibitor to enter clinical trials, raised HDL cholesterol but also cardiovascular deaths due to off-target effects [129]. Further studies with other compounds of medium potency (dalcetrapib) and high potency (evacetrapib, anacetrapib) showed no benefits in large trials [130], except that anacetrapib produced a marginal reduction in MI but not total CVD events [131].

Cardiovascular risk guidelines

All CVD guidelines agree that aggressive lipid-lowering therapy is required in management of type 2 diabetes (Figure 48.7) [3, 4, 132]. These include prescription of high-dose high-efficacy statin therapy, consideration of use of ezetimibe in ACS, and PCSK9 inhibitors in individuals intolerant to statin therapy or with residual high LDL cholesterol. Most extrapolate these recommendations to type 1 diabetes based on a small amount of evidence and consensus. All guidelines suggest an LDL cholesterol target of <2 mmol/l, but the latest data indicate that <1.5 mmol/l might be appropriate, and the European guidelines are <0.8 mmol/l in ultra-high-risk individuals with ACS and additional risk factors including diabetes. Registry studies suggest that smoking cessation and optimized glucose management are still required in individuals with type 2 diabetes even if lipids are optimized [16], but the overall trends indicate that improvements in risk factor control are translating into reduced CVD events in both type 1 and type 2 diabetes [10].

Future drug developments and drug targets

Further developments in lipid lowering include longer-acting PCSK9 inhibitors such as inclisiran, with a six-monthly dosing schedule for short-interfering RNA therapy as opposed to fortnightly for antibody-based therapies [133]. Immunization against PCSK9 may also be possible. All are capable of 50% LDL cholesterol reductions. The alternative method to reduce LDL cholesterol is to inhibit hepatic adenosine triphosphate citrate-coenzyme A lyase with bempedoic acid, which reduces LDL cholesterol by 20–25% and is likely to be most frequently used in people who are intolerant of statins and have moderate dyslipidaemia [134]. Among TG-lowering drugs, CVD outcome studies will be published on pemafibrate and on EPA derivatives. Little new is expected in HDL-raising therapies in the next few years, given the previous data on CETP inhibitors and the lack of benefit with the bromodomain and extraterminal domain (BET) inhibitor apabetalone.

Non-alcoholic fatty liver disease

There is a strong association between the presence of diabetes, especially type 2 diabetes and non-alcoholic fatty liver disease (NAFLD), and of NAFLD with CVD (Chapter 57) [135]. This reflects the role of insulin resistance and inflammation on the liver and the resultant oversynthesis and secretion of VLDL, leading to a mixed hyperlipidaemia in plasma. Many drugs used to treat insulin resistance and mixed hyperlipidaemia such as metformin, pioglitazone, or fibrates also have beneficial effects in reducing liver fat. New drugs are being developed for NAFLD and non-alcoholic steatohepatitis (NASH), with many being derived from compounds that affect the retinoid-X receptor (RXR) network [136]. Some of these drugs (e.g. obeticholic acid) have contrasting actions on plasma and liver lipid content. All these drugs require CVD outcomes trials, which will likely include individuals with type 2 diabetes and possibly some with type 1 diabetes. Table 48.1 shows the drug classes used or in development for treatment of NAFLD or NASH.

Conclusion

CVD is a very common complication of diabetes, and up to 80% of all people with diabetes will die from macrovascular complications. Lifestyle intervention is both effective and paramount to prevent and treat diabetes and its dyslipidaemia. Statins have revolutionized preventive cardiovascular medicine, and this has formed the foundation of therapeutic lipid intervention (Table 48.2). The abnormalities in lipids and lipoproteins represent only one factor among several that are responsible for the increased risk in persons with diabetes, and therefore multifactorial intervention (Figure 48.8) is required to reduce risk to that of the general population [16].

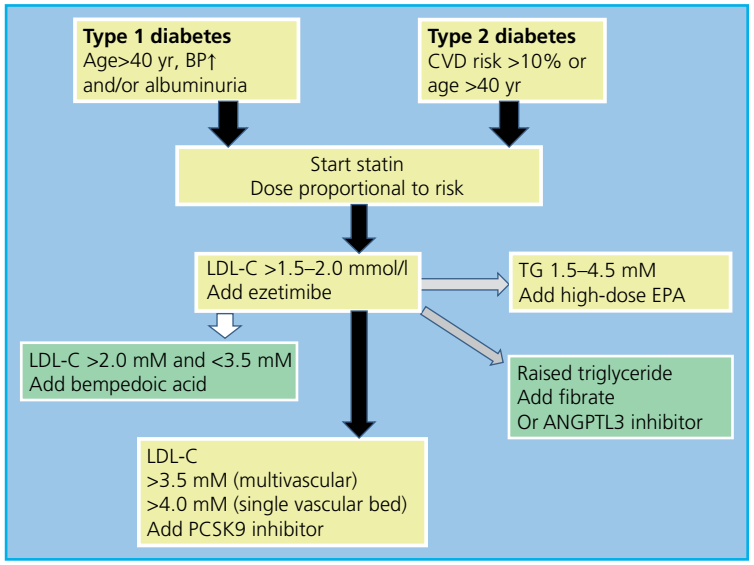

Figure 48.7 Pathways in clinical guidelines for management of lipids based on the American, European, and UK National Institute for Health and Care Excellence (NICE) recommendations. The potential position of novel therapies is indicated. The suggested cut-offs and targets may be modified to lower levels as guidelines evolve. ANGPTL3, angiopoietin-like protein 4; BP, blood pressure; CVD, cardiovascular disease; EPA, eicosapentanenoic acid; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin kexin-9; TG, triglycerides.

Table 48.1 Drug classes used (**bold**) or in development for treatment of non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH).

AMP kinase A agonists	PPAR agonists	Farnesoid-X receptor agonists	Weight-reducing agents	Anti-fibrotics
Metformin	**PPAR-γ Pioglitazone** PPAR-α/γ, e.g. saroglitazar PPAR-α/δ, e.g. elafibrinor	**Obeticholic acid** FGF-19 agonists, e.g. aldafermin	**GLP-1 receptor agonists, e.g. semaglutide** CB1 agonists, e.g. rimonabant (withdrawn)	ASK-1 inhibitors, e.g. selonsertib

ASK-1, apoptosis signal-regulated kinase-1; CB1, cannabinoid type 1; FGF-19, fibroblast growth factor 19; GLP-1, glucagon-like protein 1; PPAR, peroxisomal proliferator-activating receptor.

Table 48.2 Effects of different cardiovascular (CV) therapies on lipids and other CV risk factors and endpoint trial evidence of effects in prevention of diabetes and cardiovascular disease (CVD).

Drug/ treatment group	Component of the cardio-metabolic syndrome change (%)					Diabetes risk reduction (%)	CVD risk reduction (%)
	LDL-C decrease	HDL-C increase	TG decrease	SBP decrease	Glucose decrease		
Metformin	0–10	15	15	0–5	10	45–48	35
SU	0–5	0	0	3	0	?	20
TZD	(–5)–10	9	12	5	8	51–58	10–(+43)
GLP-1 agonist	5	(–2)	20	0	10	?	11
SGLT-2 inhibitor	(–5)	5	5	2	10–15	?	12
Statin	20–55	0–15	15–25	0	0	(–11)	20–55
Fibrate	0–10	2–16	15–24	0–8	0–6	0–23	10–34
Niacin	10–20	10–25	15–35	0	(–10)	?	22–31
Ezetimibe	20	3	8	0	0	?	6[a]
PCSK-9 inhibitor	40–65	5–7	23	0	0	0	15–20[a]
Orlistat	0–5	+3	1	1	4	43	?

Negative effects shown in brackets.
CVD, cardiovascular disease; GLP-1, glucagon-like peptide 1; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCSK-9, proprotein convertase subtilisin kexin-9; SBP, systolic blood pressure; SGLT-2, sodium–glucose cotransporter 2; SU, sulfonylurea; TG, triglycerides; TZD, thiazolidinedione.
[a]Data on ezetimibe and PCSK-9 inhibitors on cardiovascular events are only available in people already optimized on statin therapy. Effects are consistent with other LDL-C-lowering drugs in showing a relative risk reduction of 21% per 1 mmol/l LDL-C.

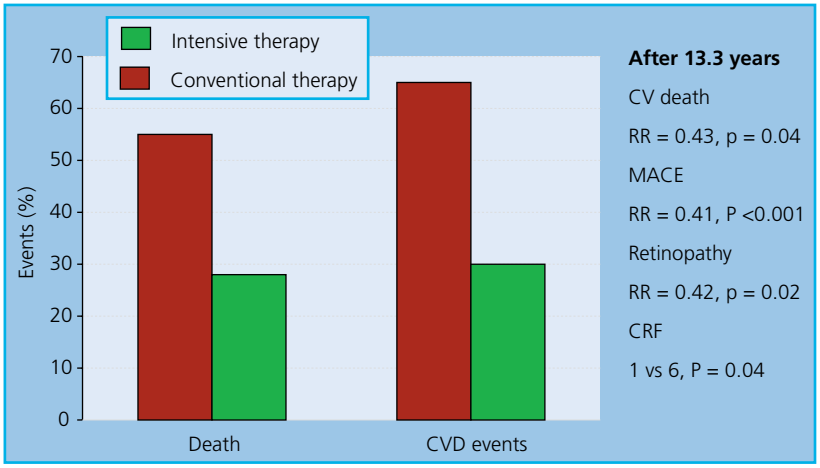

Figure 48.8 Effects of improved multiple risk factor intervention on mortality and cardiovascular events in diabetes. Steno-2: composite endpoint of death from cardiovascular causes, non-fatal myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention, non-fatal stroke, amputation, or surgery for peripheral arterial disease. CRF, chronic renal failure; CV, cardiovascular; CVD, cardiovascular disease; MACE, major adverse cardiovascular events; RR, relative risk. Source: Data from Gaede et al. 2003 [137] and Gaede et al. 2008 [138].

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49 Ischaemic Heart Disease in Diabetes

Michael Lehrke and Nikolaus Marx
Department of Internal Medicine I (Cardiology), University Hospital, RWTH Aachen University, Aachen, Germany

Key points

- People with diabetes have an increased risk of developing ischaemic heart disease.
- Glucose lowering is important for the prevention of microvascular disease in diabetes, but has only moderate effects on the prevention of macrovascular complications.
- Individuals with diabetes and high or very high cardiovascular risk, including those with atherosclerotic cardiovascular disease, should be treated with sodium–glucose cotransporter 2 inhibitors and/or glucagon-like peptide 1 receptor agonists with proven cardiovascular benefit.
- Lowering low-density lipoprotein (LDL) cholesterol is highly effective in lowering cardiovascular event risk in people with diabetes; the LDL cholesterol goal in individuals with type 2 diabetes and very high cardiovascular risk and also in those with long-standing type 1 diabetes or end-organ damage is ≤55 mg/dl (1.4 mmol/l).
- Arterial hypertension should be treated to achieve a blood pressure of ≤140/80 mmHg in people with diabetes, aiming for a systolic blood pressure of 130 mmHg and lower if tolerated, but not below 120 mmHg.
- Aspirin may be considered on an individualized basis in those at high cardiovascular risk.

Epidemiology

Ischaemic heart disease is by far the leading cause of death in people with diabetes [1]. Approximately one-third of all individuals with diabetes have atherosclerotic cardiovascular disease. Understanding the pathophysiological links between diabetes and coronary heart disease and gaining a thorough knowledge of the therapeutic options to prevent ischaemic heart disease in people with diabetes are therefore of the utmost importance.

In a 1998 landmark study [2], Haffner et al. reported that individuals with diabetes without previous myocardial infarction were at the same risk of future ischaemic heart disease events as someone with a prior myocardial infarction, but no diabetes. This observation had a major impact on clinical practice and established the concept of treating diabetes as a coronary heart disease risk equivalent. Indeed, in the current European Society of Cardiology (ESC) prevention guidelines, a similar aggressive approach to lipid lowering is recommended for those with type 2 diabetes and very high cardiovascular risk (>3 risk factors or end-organ damage), as recommended for those with established cardiovascular disease [3].

Pathophysiological perspective

Although diabetes as a clinical entity is diagnosed when glucose or glycated haemoglobin (HbA_{1c}) rises above internationally recognized thresholds, metabolic abnormalities that are associated with atherosclerosis in general, and with ischaemic heart disease in particular, typically exist for years or decades before diabetes becomes manifest [4, 5]. In the sequence of events that eventually leads to the development of diabetes, insulin resistance is an early feature. This in turn is the key pathophysiological mechanism behind the metabolic syndrome, a cluster of metabolic abnormalities including elevated glucose, dyslipidaemia, visceral obesity, and elevated blood pressure, all of which are independently linked to the development of atherosclerotic disease [4, 5]. Type 2 diabetes becomes manifest only when β-cell failure develops on the background of pre-existing insulin resistance; that is, when the demand for insulin supply caused by insulin resistance can no longer be fulfilled [4]. The atherogenic environment of multiple cardiovascular risk factors associated with the metabolic syndrome has by then typically existed for years, if not decades. From this, it is clear that cardiovascular prevention must not be delayed till the stage of established diabetes, but should take place much earlier.

As glucose levels increase during the transition from metabolic syndrome to type 2 diabetes, the cardiovascular risk becomes progressively higher. In addition to the atherogenic metabolic syndrome risk factors, elevated glucose concentrations, through oxidative stress, can cause additional harm to the endothelium [6]. Importantly, however, glucose is not the main driving force for ischaemic heart disease, as glucose-lowering strategies have been largely disappointing with respect to reducing macrovascular disease. This is an important difference in comparison with the paramount role of elevated glucose for diabetic microangiopathy, which is directly caused by elevated glucose [7].

This pathophysiology applies to type 2 diabetes, which is particularly closely linked to cardiovascular disease, but type 1 diabetes is also associated with an increased cardiovascular risk [8]. However, the timespan between the onset of diabetes and the development of ischaemic heart disease is much longer in type 1 diabetes than in type 2 diabetes. In addition to direct glucotoxicity,

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impairment of kidney function is an important mechanism linking type 1 diabetes to ischaemic heart disease risk.

Given the strong association of diabetes and cardiovascular disease, people with diabetes should be screened for the presence of atherosclerotic cardiovascular disease and heart failure, while those with heart failure or atherosclerotic cardiovascular disease should be screened for diabetes.

How can cardiovascular risk be reduced in people with diabetes?

Cardiovascular risk categorization

Recent guidelines, such as the 2019 ESC guidelines on pre-diabetes, diabetes, and cardiovascular disease, suggest classifying individuals according to their cardiovascular risk [3]. Very high-risk individuals are those with diabetes and established cardiovascular disease, as well as those with target-organ damage such as left ventricular hypertrophy or chronic kidney disease. In addition, those with diabetes and three or more major risk factors are also considered to be at very high risk, based on the observation that multiple risk factors in diabetes increase the risk, for example, for cardiovascular death [3]. People in the high-risk category are those with a diabetes duration of 10 years or longer without target-organ damage plus any additional risk factors. Finally, younger people (those with type 1 diabetes aged <35 years or type 2 diabetes aged <50 years) with a diabetes duration of <10 years and without other risk factors are considered at moderate risk. The American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) consensus report uses comparable approaches to classify individuals and stratify therapeutic strategies and goals based on these categories.

Glucose lowering

Given that diabetes is diagnosed when glucose is elevated, glucose normalization seems to be of relevance for cardiovascular risk reduction in people with diabetes. However, numerous intervention trials addressing cardiovascular risk modification by lowering of glucose have shown no benefit.

The UK Prospective Diabetes Study (UKPDS) enrolled more than 4000 individuals with newly diagnosed type 2 diabetes [9]. Among other interventions, intensified glucose lowering was compared with conventional treatment, with participants followed for over 10 years. Although the incidence of microvascular diabetes complications was significantly reduced with intensive glucose-lowering therapy, macrovascular events, in particular myocardial infarction, stroke, and peripheral arterial disease, were not significantly reduced, although there was a non-significant trend towards a lower myocardial infarction incidence in those with intensive glucose management.

Importantly, three further trials, Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE), and the Veterans Affairs Diabetes Trial (VADT), also did not show a reduction in macrovascular diabetes events with more aggressive glucose lowering [10–12].

In ADVANCE [11], more than 11 000 participants with type 2 diabetes were randomized to intensive glucose management, with the aim of lowering HbA_{1c} below 6.5% (48 mmol/mol) versus standard glucose management according to country guidelines. During a follow-up period of five years, a combined macro- plus microvascular endpoint was significantly reduced by 14%, but macrovascular events were not reduced.

Interestingly, however, when longer time periods were observed, a benefit of more intense glucose lowering has emerged in some studies. In UKPDS, a 10-year post-trial follow-up revealed significant reductions in myocardial infarction among individuals whose glucose was lowered more aggressively during the trial [13]. In ADVANCE, however, a long-term follow-up did not show a benefit with regard to major vascular events [14], whereas in VADT there was a reduction of macrovascular events after 10 years, but this was not sustained after 15-year follow-up [15].

In people with type 1 diabetes, the Diabetes Control and Complications Trial (DCCT) did not show a significant reduction in macrovascular events during the original study period [16], but a long-term follow-up reported a significant reduction in macrovascular events over a period of 17 years [17].

In the ACCORD trial [10], contrary to expectation, mortality was higher in participants receiving more intense glucose lowering. This suggests that overly aggressive glucose lowering can cause harm in people with diabetes, possibly through weight gain and increased risk for hypoglycaemia. Hypoglycaemia is a severe stressor leading to an adrenergic and inflammatory response and has been linked to increased risk of cardiovascular events [18]. Furthermore, repolarization abnormalities of the heart occur in response to hypoglycaemia with the potential for malignant arrhythmia. Although this provides a rationale for the increased mortality observed in the ACCORD trial, causality has not been proven. Other studies using insulin or sulfonylurea, both hypoglycaemia-prone medications, have not reported increased cardiovascular risk despite an increased occurrence of hypoglycaemia during the trials, questioning direct causality [19, 20]. However, hypoglycaemia impairs life quality and should be avoided whenever possible.

Meta-analysis of interventional glucose-lowering trials have identified subgroups of individuals deriving macrovascular benefit from intensive glucose management. Importantly, these were younger persons with lower HbA_{1c}, early stages of diabetes, and absence of micro- or macrovascular disease [21]. As a consequence, individualized HbA_{1c} treatment goals have been recommended, which should consider existing comorbidities, life expectancy, and individual preference [3]. The ADA recommends an HbA_{1c} of <7.0% (53 mmol/mol) for the prevention of diabetes complications [22].

The general lack of effect of HbA_{1c} reduction on cardiovascular risk shifted attention to the cardiovascular benefit of individual glucose-lowering drugs and drug classes. When a 2008 meta-analysis of the study programme of rosiglitazone, a peroxisome proliferator-activated receptor-γ (PPARγ) agonist, suggested that the drug caused cardiovascular harm, the US Food and Drug Administration (FDA) mandated that cardiovascular outcome trials of all new anti-diabetes drugs should be undertaken to demonstrate that the drug did not increase cardiovascular risk [23]. As a consequence, a multitude of cardiovascular endpoint trials have been performed, which have reshaped the evidence of diabetes therapy in those with high and very high cardiovascular risk. Sodium–glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists have emerged as two drug classes that improve cardiovascular outcomes independent of HbA_{1c} (Chapters 35 and 36). In addition, dipeptidyl peptidase 4 (DPP-4) inhibitors, sulfonylureas, and basal insulin provide cardiovascular safety in treatment periods up to 6.3 years.

The concept of metformin as the first-line therapy in people with type 2 diabetes has recently been challenged in the 2019 ESC

guidelines on diabetes, pre-diabetes, and cardiovascular diseases. Evidence for the use of metformin derived from the UKPDS trial, in which a subgroup of 342 obese individuals with newly diagnosed diabetes treated with metformin had a 39% risk reduction of myocardial infarction and 36% risk reduction in total mortality [24]. The subgroup design with small sample size, a limited number of events, and selected baseline characteristics, however, precludes a generalization of these findings. This has led the ESC to recommend SGLT-2 inhibitors or GLP-1 receptor agonists as new first-line therapy in those with diabetes and high or very high cardiovascular risk, while metformin was only recommended as first-line therapy in those with moderate cardiovascular risk, resembling the UKPDS population [3]. By contrast, the ADA/EASD still recommend metformin as first-line therapy for most people with type 2 diabetes.

Cardiovascular risk reduction has also been demonstrated for pioglitazone. In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE), 5238 people with type 2 diabetes and macrovascular disease were randomized to either pioglitazone 45 mg daily or placebo [25] and followed up for three years. The primary endpoint of PROACTIVE was broad, including, in addition to death, non-fatal myocardial infarction and stroke, three-point major adverse clinical event (MACE), acute coronary syndrome, leg amputation, coronary revascularization, and revascularization of peripheral arteries. With regard to the primary endpoint, the risk reduction with pioglitazone was non-significant; however, when the more clinically relevant secondary endpoint of three-point MACE was considered, a significant 16% event reduction was observed with pioglitazone compared with placebo. Similar results were found in the Insulin Resistance Intervention after Stroke (IRIS) trial, in which 3876 individuals with pre-diabetes were treated with pioglitazone versus placebo following an ischaemic neurological event. Pioglitazone significantly reduced three-point MACE by 24% [26].

The Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial randomized people to insulin glargine or standard care and showed neither a decrease nor increase in total cardiovascular events or ischaemic heart disease events with insulin glargine [19].

Following the 2018 FDA recommendations, several cardiovascular safety trials were published. Four large cardiovascular outcome trials compared DPP-4 inhibitors with placebo. DPP-4 inhibitors increase the serum levels of native GLP-1 by inhibiting the cleaving enzyme DPP-4. In all of these trials (Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus–Thrombolysis In Myocardial Infarction [SAVOR-TIMI 53] with saxagliptin vs placebo [27]; Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care [EXAMINE] with alogliptin vs placebo [28]; Trial Evaluating Cardiovascular Outcomes with Sitagliptin [TECOS] with sitagliptin vs placebo [29]; and Cardiovascular and Renal Microvascular Outcome Study with Linagliptin [CARMELINA] with linagliptin vs placebo [30]), the cardiovascular safety of DPP-4 inhibitors was confirmed, but none of the agents tested reduced cardiovascular events for three-point MACE (SAVOR-TIMI 53, EXAMINE, CARMELINA) or four-point MACE (TECOS). Notably, in one of the trials (SAVOR-TIMI 53), saxagliptin increased the risk for hospitalization for heart failure, an effect that was not seen with any of the other agents, suggesting that this is not a class effect but related to the compound itself or a chance finding [27].

The Cardiovascular Outcome Study of Linagliptin vs Glimepiride in Type 2 Diabetes (CAROLINA) directly compared the DPP-4 inhibitor linagliptin with the sulfonylurea glimepiride in respect to cardiovascular outcomes in people with relatively early type 2 diabetes and cardiovascular risk factors or established atherosclerotic cardiovascular disease. No difference in cardiovascular safety was observed between the two drugs despite glimepiride causing more hypoglycaemia (37.7% vs 10.6%) [20].

Sodium–glucose cotransporter 2 inhibitors

SGLT-2 inhibitors inhibit glucose reabsorption in the proximal tubal, thus leading to glucosuria and lowering of blood glucose levels. Four placebo-controlled cardiovascular outcome trials examined the effect of SGLT-2 inhibitors on the three-point MACE endpoint. Empagliflozin in the Empagliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients–Removing Excess Glucose (EMPA-REG) OUTCOME trial [31] and canagliflozin in the Canagliflozin Cardiovascular Assessment Study (CANVAS) trial significantly reduced three-point MACE [32]. In addition, canagliflozin significantly reduced three-point MACE in people with diabetes and nephropathy (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy [CREDENCE] trial) [33]. Dapagliflozin Effect on CardiovascuLAR Events (DECLARE) examined the effect of dapagliflozin versus placebo in people with diabetes and did not find a significant reduction of three-point MACE, most likely due to the lower risk population; approximately 60% of participants did not have cardiovascular disease but did have multiple risk factors [34]. However, all three agents showed a significant reduction of the combined endpoint of hospitalization for heart failure or cardiovascular death, suggesting that the beneficial effect of SGLT-2 inhibitors is most likely mediated through a reduction of heart failure–related events (Chapter 50). This has been confirmed by the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, which showed that dapagliflozin led to a reduction of the combined endpoint of worsening of heart failure or cardiovascular death versus placebo in people with heart failure with reduced ejection fraction (HFrEF), with or without diabetes [35]. In addition, in the EMPA-REG OUTCOME trial, empagliflozin significantly reduced all-cause mortality compared to placebo [31].

In the Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants with Vascular Disease (VERTIS CV) trial [36], ertugliflozin was compared with placebo in 8238 individuals with type 2 diabetes and established cardiovascular disease. This turned out to be the only SGLT-2 inhibitor cardiovascular outcome trial to miss its primary superiority endpoint of cardiovascular death. Hospitalization for heart failure, however, occurred less frequently in the ertugliflozin group (hazard ratio [HR] 0.70; 95% confidence interval [CI] 0.54 to 0.090) [36]. In the randomized, placebo-controlled DApagliflozin and Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) trial, the effects of dapagliflozin on morbidity and mortality were studied in people with chronic kidney failure (mean estimated glomerular filtration rate [eGFR] of 43 ml/min/1.73 m^2). The trial was performed in a population of people both with and without diabetes. Dapagliflozin, compared to placebo, led to a significant reduction in the primary composite endpoint of sustained ≥50% eGFR decline, end-stage kidney disease, renal or cardiovascular death, as well as hospitalization for heart failure [37].

In the most recent meta-analysis of SGLT-2 inhibitor cardiovascular outcome trials [38, 39], relative risk reductions for MACE, cardiovascular death, hospitalization for heart failure, and chronic kidney disease progression were estimated to be 10%, 15%, 32%, and 38%, respectively. For MACE, the benefit was only significant in those with established atherosclerotic cardiovascular disease. In contrast, hospitalization for heart failure was reduced in individuals both with and without atherosclerotic cardiovascular disease, and with or without heart failure.

Glucagon-like peptide 1 receptor agonists

Eight large cardiovascular outcome trials with GLP-1 receptor agonists have been published in full so far. Two of these trials confirmed cardiovascular safety by showing non-inferiority versus placebo, while in six trials a reduction of cardiovascular endpoints has been observed [40].

Confirmation of cardiovascular safety but no reduction of cardiovascular risk was shown in the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) [41] and the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) [42]. In ELIXA, people with a recent acute coronary syndrome were randomized to lixisenatide or placebo and followed over a median of 2.1 years. Lixisenatide was non-inferior to placebo, but did not show a reduction in the primary endpoint of three-point MACE [41]. EXCSEL examined the effect of extended-release exenatide versus placebo in more than 14 000 individuals and showed a non-significant trend towards reduction of three-point MACE with an HR of 0.91 (95% CI 0.83 to 1.0). Exenatide reduced all-cause mortality with an HR of 0.86 (95% CI 0.77 to 0.97), but based on the hierarchical statistical analysis plan, this result has to be considered hypothesis generating [42].

Six other trials with GLP-1 receptor agonists showed a reduction in cardiovascular endpoints. Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) assessed the effect of liraglutide versus placebo over a median follow-up of 3.8 years and showed that liraglutide treatment not only reduced three-point MACE, but also led to a significant reduction in cardiovascular death and all-cause mortality [43]. In the Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with T2DM (SUSTAIN-6), once-weekly injectable semaglutide significantly reduced three-point MACE over a median follow-up of 2.1 years with a significant relative risk reduction of 27% ($p = 0.02$). This effect of three-point MACE was mainly driven by a significant reduction of stroke and a trend towards a reduced incidence of myocardial infarction [44]. Albiglutide, another GLP-1 receptor agonist currently not marketed, was tested versus placebo in HARMONY OUTCOMES. Over a median follow-up of 1.6 years, albiglutide led to a significant 22% reduction of three-point MACE and a 25% relative risk reduction of myocardial infarction [45]. The effect of dulaglutide, a long-acting GLP-1 receptor agonist, on cardiovascular events was assessed in Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) versus placebo. Over a median follow-up of 5.7 years, a significant reduction of three-point MACE as well as a significant reduction of stroke was observed in those treated with dulaglutide [46]. The Peptide Innovation for Early Diabetes Treatment (PIONEER-6) trial assessed the effect of oral semaglutide in a phase 2 study versus placebo and over a median follow-up of 1.3 years, this GLP-1 receptor agonist did not reduce three-point MACE, but led to a 51% relative reduction of cardiovascular death [47]. In addition, oral semaglutide reduced all-cause mortality. Effect of Efpeglenatide on Cardiovascular Outcomes (AMPLITUDE-O) investigated cardiovascular outcomes of the exendin-based weekly GLP-1 receptor agonist efpeglenatide. During a treatment period of 1.81 years, efpeglenatide reduced MACE significantly by 27%, independent of SGLT-2 inhibitor use, which was prescribed present in 15% of the population [48]. In all of these trials, only albiglutide significantly reduced hospitalization for heart failure, while the effect on heart failure hospitalization was neutral in the other trials.

These GLP-1 receptor agonist cardiovascular outcome trials differ with respect to the population examined, ranging from established cardiovascular disease in all individuals enrolled in ELIXA and HARMONY, to the population in REWIND where only 31% had established cardiovascular disease, while the remainder were included based on multiple risk factors. One of the questions arising from these cardiovascular outcome trials with GLP-1 receptor agonists is whether the beneficial effects seen are only present in those with established cardiovascular disease, or whether people with type 2 diabetes and multiple risk factors might benefit to a similar extent. A recent meta-analysis published by Masiko et al. suggests that there is no difference in benefit of GLP-1 receptor agonists on three-point MACE between people with or without cardiovascular disease, indicating consistent benefits not only in individuals with established cardiovascular disease, but also importantly in those with multiple risk factors in the absence of clinically apparent cardiovascular disease.

These trials have had a major impact on recent guidelines. The 2019 ESC guidelines on diabetes and cardiovascular disease recommend the use of a GLP-1 receptor agonist with proven cardiovascular benefit in individuals at high or very high cardiovascular risk. This group includes individuals with multiple risk factors or atherosclerotic cardiovascular disease (very high risk or those with a single risk factor) [3]. The ADA/EASD guidelines suggest prescribing these agents for individuals with established cardiovascular disease and those at high risk of cardiovascular disease [49].

Lipid management

Lipids play an essential role in the development of ischaemic heart disease, and therefore are a central target in preventive cardiology, in particular in people with diabetes (Chapter 48). Lipid metabolism in people with diabetes is characterized by hypertriglyceridaemia, low high-density lipoprotein (HDL) cholesterol, and small dense low-density lipoprotein (sdLDL) particles. The absolute levels of LDL cholesterol do not differ between people with and without type 2 diabetes [43].

Owing to insulin resistance, free fatty acids are released from adipose tissue and used by the liver to synthesize triglyceride-rich very low-density (VLDL) particles. Lipases hydrolyse triglycerides from VLDL particles, creating intermediate-density lipoprotein (IDL) particles and finally low-density lipoprotein (LDL) particles, which return to the liver by LDL receptor binding and secretion of cholesterol in the form of bile acids. Mediated by the enzyme cholesteryl ester transfer protein (CETP), triglyceride-rich lipoproteins are exchanged for cholesterol from LDL and HDL particles. LDL and HDL particles thus lose cholesterol and receive triglycerides in turn. These triglycerides are then removed by the action of hepatic lipase, rendering both LDL and HDL smaller and denser. Smaller HDL particles are more rapidly cleared by the kidney, which explains the low HDL cholesterol of individuals with type 2 diabetes; sdLDL particles are particularly atherogenic and explain in part why people with diabetes already at moderate LDL cholesterol levels are at a high risk of cardiovascular events.

Epidemiological and genetic studies confirm triglyceride-rich lipoproteins and their remnant particle as important contributors to cardiovascular disease [50]. Most triglycerides are carried by VLDL and VLDL remnants, with the latter being cholesterol enriched and sufficiently small to penetrate the vessel wall. Each triglyceride-rich lipoprotein and LDL carries one apolipoprotein B (ApoB). Circulating ApoB therefore indicates the number of atherogenic lipoproteins, while non-HDL cholesterol (total cholesterol minus HDL cholesterol) summarizes the atherogenic cholesterol content [51]. Both measures are used to guide lipid therapy [52]. While ApoB can substitute for the use of LDL cholesterol, non-HDL cholesterol is considered a secondary therapeutic target after reaching sufficient LDL cholesterol lowering. Despite the relevance of triglyceride-rich lipoproteins for atherosclerotic disease, cardiovascular risk reduction can most efficiently be reached by LDL cholesterol lowering, most likely reflecting the smaller particle size and efficacy in penetrating the arterial wall [52]. A large meta-analysis enrolling over 18 600 people with diabetes from 14 randomized trials of statins showed that for every 1 mmol LDL cholesterol reduction, the risk of myocardial infarction was reduced by 22%, which was not significantly different from the 19% event reduction achieved with the same amount of LDL reduction in individuals without diabetes [44]. The more LDL cholesterol is reduced, the better for cardiovascular risk reduction [45], and this holds true for individuals with and without diabetes and/or elevated triglyceride levels [53]. The absolute benefit of LDL cholesterol lowering is most pronounced in those with high baseline cholesterol, in addition to high cardiovascular risk.

The ESC guidelines recommend that all individuals with diabetes be treated to an LDL cholesterol target of <2.6 mmol/l (100 mg/dl). This should be intensified in individuals with high cardiovascular risk (no end-organ damage but diabetes duration ≥10 years and any additional risk factor) to an LDL cholesterol target of <1.8 mmol/l (<70 mg/dl). Additional intensification is recommended in case of very high risk (with target-organ damage, or at least three major risk factors, or early onset of type 1 diabetes with duration >20 years) to an LDL cholesterol target of <1.4 mmol/l (55 mg/dl) and a secondary target of non-HDL cholesterol of < 2.2 mmol/l (85 mg/dl).

Low-density lipoprotein cholesterol lowering

LDL cholesterol lowering should primarily be achieved with statin therapy, which lowers LDL cholesterol by 30–50%. Individuals not reaching LDL cholesterol targets with maximal tolerated statin therapy should receive additional ezetimibe treatment, which lowers LDL cholesterol by 15–20% [52, 54]. Subgroup analysis of the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) trial suggested that people with diabetes benefited particularly from LDL cholesterol lowering with ezetimibe [55]. Lowering of LDL cholesterol with a statin or with additional ezetimibe treatment thus has proven efficacy in reducing cardiovascular events, in particular in those with diabetes.

Escalation of therapy can also be reached by proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition. Currently two PCSK9-directed monoclonal antibodies (evolocumab and alirocumab) are available, each resulting in additional LDL cholesterol lowering of 50–60% in individuals with or without diabetes [56, 57]. Both antibodies reduced cardiovascular risk by 15% in high-risk individuals with established cardiovascular disease [58, 59]. A comparable efficacy was found in people with and without diabetes, while absolute risk reduction was more pronounced in individuals with diabetes, reflecting their greater baseline risk [60]. Further inhibition of PCSK9 can be achieved with small interfering RNA molecules that inhibit hepatic protein synthesis. Inclisiran is currently being developed for subcutaneous application every six months, with additional LDL cholesterol lowering of approximately 50% in individuals on statin therapy [61]. Novel therapies for LDL cholesterol reduction further include bompedonic acid. This pro-drug is metabolized to a competitive inhibitor of adenosine triphosphate (ATP)-citrate lyase, depleting intracellular cholesterol content with LDL receptor induction and subsequent LDL cholesterol lowering of 15–30% [62]. The Cholesterol Lowering via Bempedoic acid, an ACL-inhibiting Regimen (CLEAR) Outcomes study is evaluating the cardiovascular efficacy of bempedoic acid in 12 600 statin-intolerant individuals who were intolerant of statins and is expected to report in 2023 (NCT02993406).

Treatment of hypertriglyceridaemia

Treatment of hypertriglyceridemia simultaneously reduces ApoB and non-HDL cholesterol and should primarily be achieved by lifestyle and dietary interventions. Pharmacotherapy can be performed with fibrates or nicotinic acid, both reducing triglycerides by 20–50% [63]. Randomized trials found that fibrates and nicotinic acid lowered cardiovascular risk in the pre-statin area [64], but this was not replicated in more recent trials providing statin background therapy [65–67]. An important limitation of these trials, however, is that inclusion of participants was not limited to those with elevated triglyceride or low HDL cholesterol. Subgroup analysis suggests that fibrates may lower cardiovascular risk in people with elevated triglycerides or low HDL cholesterol despite concomitant statin therapy [68]. The Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) trial, which recruited 10 497 statin-treated persons with type 2 diabetes and high triglycerides, did not show a reduction of the combined primary efficacy end point (non-fatal myocardial infarction, ischaemic stroke, coronary revascularization, or death from cardiovascular causes) by pemafibrate compared to placebo [69].

Lowering of triglycerides can also be achieved with high-dose omega-3-fatty acids (>2 g/d). Lower-dose omega-3-fatty acids (1 g/d) have not been found to reduce cardiovascular risk [64]. High-dose icosapent ethyl (4 g/d) importantly reduced cardiovascular events (three-point MACE) by 26% (HR 0.74; 95% CI 0.65 to 0.83) in 8179 statin-treated high-risk individuals with elevated triglycerides, with similar reductions in those with or without diabetes [70]. These results were not confirmed in the Statin Residual Risk Reduction with EpaNova in High Cardiovascular Risk Patients with Hypertriglyceridaemia (STRENGTH) trial; treatment with a combination of omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid; 4 g/d) did not reduce cardiovascular risk in >13 000 individuals with high cardiovascular risk [71]. Additional studies are consequently needed to evaluate the cardiovascular benefit of high-dose omega-3-fatty acids in people with high triglyceride levels.

Novel triglyceride-lowering therapies include strategies to reduce ApoC-III and angiopoietin-like protein 3 (ANGPTL-3), which have both been linked to cardiovascular risk in genetic studies [72, 73]. ApoC-III travels with triglyceride-rich lipoproteins and inhibits lipoprotein lipase [74]. The antisense oligonucleotide volanesorsen reduces triglyceride levels by approximately 80% and was recently approved by the European Medical Agency for the treatment of familial chylomicronaemia syndrome [75]. Adverse

events include thrombocytopaenia and flu-like symptoms [75]. ANGPTL-3 impairs VLDL clearance and HDL particles by inhibition of lipoprotein and endothelial lipase activity. Reduction of ANGPTL-3 has been obtained with a monoclonal antibody (evinacumab) and antisense oligonucleotide (IONIS-ANGPTL-3-LRx), both of which reduce triglycerides by 60–70% and LDL cholesterol by 20–30% [76, 77].

Targeting high-density lipoprotein cholesterol

HDL cholesterol is a strong negative predictor of cardiovascular risk. Still, neither genetic nor pharmacological interventions have found that modification of HDL levels reduces cardiovascular risk [78]. HDL is a complex molecule comprising multiple lipoproteins and recent evidence suggests that HDL composition and functionality determine cardiovascular risk rather than particle number. This mostly refers to the capacity of HDL to guide reverse cholesterol transport, which is initiated by ApoA-1 serving as an acceptor for the cellular cholesterol [79]. New early therapeutic avenues include recombinant HDL or ApoA-1 particles in addition to lecithin-cholesterol acyl transferase (LCAT) activators.

Blood pressure management

Blood pressure and the management of hypertension in people with diabetes are discussed in more detail in Chapter 47 [80]. The 2018 ESC Guidelines for the Management of Arterial Hypertension recommend a blood pressure target of ≤140/80 mmHg in people with diabetes. Provided that treatment is well tolerated, treated systolic blood pressure targets of <130 mmHg should be considered because of the benefits for stroke prevention. Achieved systolic blood pressure values of <120 mmHg should be avoided [80].

In the blood pressure arm of the ACCORD trial, 4700 individuals with type 2 diabetes were randomized to a systolic blood pressure target <120 mmHg or standard therapy with a systolic blood pressure target of <140 mmHg [81]. Mortality and ischaemic heart disease were not reduced by more aggressive blood pressure lowering, but stroke events fell by 47%. More intense therapy, however, was associated with more arrhythmic events, hypokalaemia, and hypotension, and so this aggressive treatment target cannot be generally recommended. Another study found that in people with diabetes and established ischaemic heart disease, overly intense blood pressure lowering led to an increased mortality risk. In individuals with systolic blood pressure below 110 mmHg, mortality was significantly increased compared with those with systolic blood pressure between 125 and 130 mmHg [82]. In the VADT [83], a significant increase in cardiovascular event risk was observed when the diastolic blood pressure was lowered to <70 mmHg. For people with diabetes at high risk of cardiovascular events, in particular for those with established coronary artery disease, extremely low blood pressure targets therefore do not appear warranted.

Aspirin and anticoagulation

For many years it has been largely accepted that aspirin therapy should be employed only in secondary prevention, because of the risk-to-benefit ratio when used in primary prevention. In the newly reported A Study of Cardiovascular Events iN Diabetes (ASCEND) trial [84] of aspirin 100 mg/d against placebo in 15 480 individuals with diabetes, but without CVD, a 12% reduction in cardiovascular outcomes with a 4% bleeding risk was observed, results similar to previous meta-analyses and smaller datasets [85]. These data led to the recommendation that aspirin at a dose of 75–160 mg/d is recommended as secondary prevention in persons with diabetes. Treatment with a P2Y12 receptor blocker (ticagrelor or prasugrel) and aspirin is recommended for individuals with diabetes and acute coronary syndrome for one year, and in those who undergo percutaneous cardiac intervention or coronary artery bypass grafting.

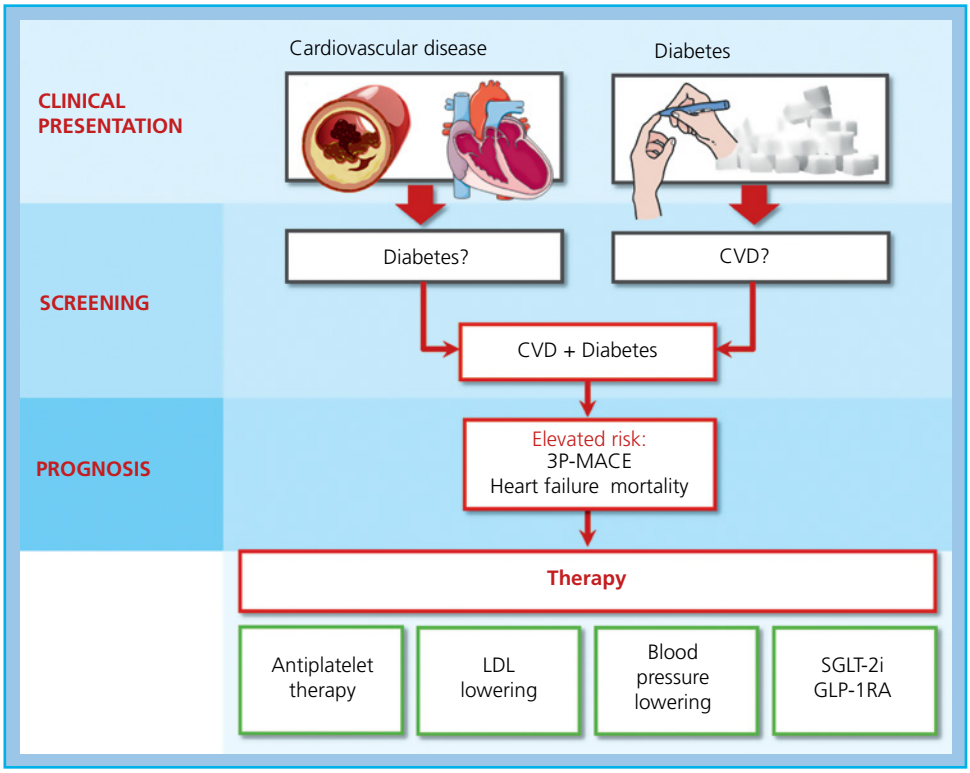

Figure 49.1 The four pillars of cardiovascular disease prevention in people with diabetes. 3P-MACE, three-point major adverse cardiovascular event; CVD, cardiovascular disease; GLP-1RA, glucagon-like peptide 1 receptor agonist; LDL, low-density lipoprotein; SGLT-2i, sodium–glucose cotransporter 2 inhibitor.

In the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial of 27 395 individuals with stable atherosclerotic cardiovascular disease [86], the combination of low-dose aspirin (100 mg daily) plus low-dose rivaroxaban (2.5 mg twice daily) was significantly superior to aspirin alone in preventing myocardial infarction, stroke, or cardiovascular death. In a subgroup of 7240 individuals, of whom 44% had diabetes, followed for 23 months, there was a significant reduction in major limb events (HR 0.54), leading to the recommendation that the combination of rivaroxaban and aspirin should be considered in individuals with diabetes and lower-extremity arterial disease.

Overall, cardiovascular risk reduction in individuals with diabetes and ischaemic heart disease is mainly based on four pillars, and the implementation of evidence-based therapies is of the utmost importance to improve the prognosis of these individuals [87] (Figure 49.1).

Multimodal therapy of cardiovascular risk factors in type 2 diabetes

Treatment of people with type 2 diabetes requires multimodal management of cardiovascular risk factors. The effectiveness of this approach was demonstrated in the Steno-2 study, in which intensified intervention of blood glucose, blood pressure (use of renin–angiotensin system blockers), aspirin, and lipid-lowering agents led to a 59% reduction of cardiovascular events and a 46% reduction of mortality during a follow-up period of 13.3 years [88].

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50 Heart Failure and Diabetes

Ambarish Pandey[1], Kershaw V. Patel[2], and Subodh Verma[3]

[1] Division of Cardiology, Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX, USA
[2] Department of Cardiology, Houston Methodist DeBakey Heart and Vascular Center, Houston, Texas, USA
[3] Division of Cardiac Surgery, St Michael's Hospital, University of Toronto, Toronto, ON, Canada

Key points

- Diabetes is associated with elevated risk for the development of heart failure.
- Hyperglycaemia, lipotoxicity, inflammation, and abnormal myocardial metabolism contribute to the underlying pathophysiology of heart failure development in diabetes.
- People with comorbid heart failure and diabetes have worse outcomes, including functional status, hospitalization, and mortality, compared with those with heart failure without diabetes.
- Several risk scores are available to estimate the risk of developing heart failure among people with diabetes.
- Clinical trials of sodium–glucose cotransporter 2 (SGLT-2) inhibitors initially demonstrated consistent benefits for heart failure prevention and later revealed improved cardiovascular outcomes among people with prevalent heart failure.
- The beneficial effects of β-blockers, renin–angiotensin system inhibitors, mineralocorticoid receptor antagonists, and SGLT-2 inhibitors for managing heart failure with reduced ejection fraction are consistent among people irrespective of diabetes status.
- Several factors should be considered when selecting anti-diabetes medications, including the risk of developing heart failure, history of heart failure, and left ventricular ejection fraction.

The relationship between diabetes and heart failure is well-recognized [1]. Dating back to the nineteenth century, diabetes was primarily considered a metabolic disorder characterized by hyperglycaemia, and its cardiovascular complications were just starting to be acknowledged. Growing evidence suggested that cardiovascular disease developed over time in this population, but excess mortality observed in diabetes limited the evaluation of long-term complications. Survival of people with diabetes was extended after the discovery and development of insulin, which facilitated the investigation of long-term diabetes-related complications. In 1954, Lundbaek reported abnormalities in the myocardium of older people with diabetes [2]. A landmark study was published in 1972 by Rubler et al. detailing the post-mortem findings of four individuals with diabetes-related complications without coexisting hypertensive, valvular, and congenital heart disease [3]. The term diabetic cardiomyopathy was used to describe the abnormalities in myocardial structure and function observed in people with diabetes in the absence of alternative causes. The contribution of diabetes to heart failure risk was further supported by epidemiological evidence from the Framingham Heart Study, demonstrating that diabetes was associated with heart failure risk after accounting for cardiovascular disease risk factors [4].

Contemporary studies confirmed and extended the findings from prior investigations examining the link between diabetes and heart failure. The epidemiology for both conditions has evolved significantly, and their impact on one another compounds the growing burden of diabetes and heart failure. Among people with heart failure, the presence of diabetes is associated with a worse prognosis compared with those without diabetes [5]. Similarly, in people with diabetes, the presence versus absence of heart failure is associated with adverse outcomes [5]. These comorbid diseases not only contribute to the prognosis of each other, but therapies targeting these conditions influence one another. Cardiovascular outcome trials of medications used to manage hyperglycaemia in diabetes revealed safety concerns such that certain agents increased the risk of hospitalization for heart failure while others improved outcomes [6]. The purpose of this chapter is to describe the overlapping epidemiology, pathophysiology, outcomes, and treatment options for diabetes and heart failure. Type 2 diabetes accounts for most diabetes cases and will be the focus of the chapter.

Two epidemics: diabetes and heart failure

Epidemiology of diabetes and heart failure

The worldwide prevalence of diabetes increased from 285 million in 2009 to 425 million in 2017 [7]. In 2019, diabetes affected 463 million people worldwide, with projected growth to 700 million by 2045. The diagnostic criteria for diabetes has been updated over the years, but this is unlikely to explain the dramatic increase in its burden. In the USA, diabetes affects more than 10% of the population and pre-diabetes, a condition of hyperglycaemia below diagnostic thresholds for diabetes, affects approximately one-third of adults [8]. In mid-life, at age 45 years, the lifetime risk of progression from pre-diabetes to diabetes is 74% [9]. Among individuals

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born in 2000 in the USA, the lifetime risk for developing diabetes is 33% in men and 39% in women [10].

Similar alarming trends have been observed in the burden of heart failure. The global prevalence of heart failure is ~12% [11]. The lifetime risk of developing heart failure is high, at ~24–27% at 45 years of age [12]. Across heart failure subtypes, the lifetime risk of heart failure with preserved ejection fraction (HFpEF) was similar among people with and without diabetes at 10–12%. In contrast, the lifetime risk of heart failure with reduced ejection fraction (HFrEF) was 60% higher in people with versus without diabetes (11.6% vs 7.4%). The older population accounts for approximately three-quarters of heart failure hospitalizations [13, 14]. The burden of heart failure has grown in the setting of declining incidence, suggesting improved survival with this chronic condition. Among people with diabetes, heart failure incidence has decreased compared to those without diabetes among older individuals [15]. The availability and use of effective preventive therapies for heart failure in diabetes may be contributing to the declining incidence of heart failure [16]. Furthermore, diabetes and heart failure commonly coexist, and the prevalence of one is higher when the other is present. For example, the prevalence of diabetes among people hospitalized with heart failure is more than 40%, which is nearly four times that observed in the general population [17]. From 2005 to 2014, the prevalence of diabetes in both heart failure subtypes appeared stable in the community [18]. Similarly, the prevalence of heart failure in diabetes is up to 20%, which is approximately four times the rate observed in the community [19]. These excess rates of coexisting diabetes and heart failure suggest interrelated pathophysiology between two cardiometabolic diseases.

Diabetes is a risk factor for heart failure and subclinical abnormalities

In the Framingham Heart Study, the risk of developing heart failure was 2–5 times higher among adults with versus without diabetes [4]. The elevated risk of heart failure observed in diabetes persisted after accounting for differences in risk factors. Unlike atherosclerotic cardiovascular diseases such as myocardial infarction, the risk of heart failure remains elevated despite control of risk factors, including haemoglobin A1c (HbA_{1c}), low-density lipoprotein cholesterol, blood pressure, albuminuria, and smoking, compared with adults without diabetes [20]. The residual risk of heart failure is greatest in young adults, emphasizing the importance of developing novel and sustainable heart failure–prevention strategies.

Heart failure develops over a series of several intermediate high-risk phenotypes. The presence of diabetes is associated with these subclinical cardiac abnormalities, including chronic myocardial injury and adverse cardiac remodelling [21, 22]. Across the glycaemic spectrum, hyperglycaemia is associated with greater left ventricular mass, and worse left ventricular systolic and diastolic function [21, 22]. The subtle, subclinical abnormalities in cardiac structure and function among people with diabetes identify an intermediate at-risk stage in the pathway to heart failure development that is often referred to as diabetic cardiomyopathy in the literature. While there is no consensus regarding its definition, recent epidemiological studies have used echocardiographic evidence of left ventricular hypertrophy, diastolic dysfunction, or elevated natriuretic peptide levels to define diabetic cardiomyopathy. The burden of diabetic cardiomyopathy in the community ranges from 12% to 67%, depending on the criteria used for its definition [23]. Presence of diabetic cardiomyopathy is independently associated with an increased risk of heart failure development, even in the absence of other cardiovascular risk factors. Thus, diabetic cardiomyopathy identifies a potentially reversible intermediate stage in the development of heart failure and may be a potential target for therapeutic intervention. To this end, results from studies evaluating the role of different pharmacotherapies in preventing heart failure hospitalization among individuals with diabetic cardiomyopathy are awaited.

Diabetes and other heart failure risk factors

People with diabetes commonly have several comorbid cardiovascular disease risk factors, and this multimorbidity contributes to the excess risk of adverse outcomes, including heart failure (Figure 50.1). Hypertension, obesity, dyslipidaemia, and kidney disease are common conditions found in people with diabetes [24].

Hypertension

Hypertension is one of the commonest risk factors observed in diabetes, with comorbid rates of ~80% (Chapter 47) [24]. Both diseases exert adverse effects on the myocardium and lead to coronary artery disease, further exacerbating myocardial ischaemia and maladaptive cardiac remodelling [25]. The multiplicative effects of hypertension and diabetes may be explained by several mechanisms:

- Differential vascular remodelling is observed in hypertension (eutrophic) and diabetes (hypertrophic), which may lead to amplified atherosclerosis and myocardial ischaemia.
- Impaired coronary flow reserve leads to heart failure, and hypertension and diabetes may synergistically worsen functional circulation [26]. Endothelial dysfunction is observed in each disease separately, but together there is a worsening of coronary flow reserve through mechanisms independent of endothelial dysfunction.
- The sympathetic tone may be exacerbated by two triggers in hypertension and diabetes, leading to neurohormonal dysregulation, cardiac remodelling, and heart failure.

Dyslipidaemia

An abnormal lipid profile is observed in approximately three-quarters of individuals with diabetes (Chapter 48) [24]. People with diabetes have a typical pattern of low high-density lipoprotein cholesterol and elevated triglyceride levels, which is termed diabetes-related dyslipidaemia [27]. The dyslipidaemia in diabetes likely

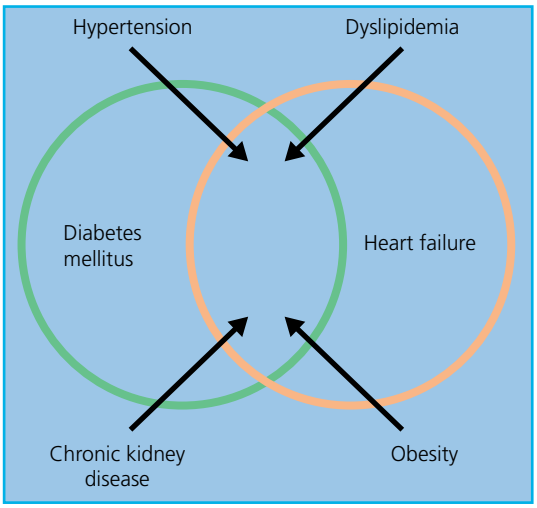

Figure 50.1 Overlapping epidemiology of diabetes, heart failure, and shared risk factors.

contributes to the risk of heart failure through multiple pathways. Dyslipidaemia may have a direct impact on heart failure risk, as low high-density lipoprotein cholesterol and elevated non-high-density lipoprotein cholesterol are associated with excess heart failure risk after accounting for risk factors, including myocardial infarction [28]. Additionally, diabetes-related dyslipidaemia is particularly pro-atherogenic, leading to coronary atherosclerosis, ischaemic heart disease, and downstream risk of heart failure.

Chronic kidney disease

Diabetes is the leading cause of chronic kidney disease, and each condition affects the other (Chapter 44) [29]. Diabetes-related kidney disease is based on chronic kidney disease, assessed by glomerular filtration rate and albuminuria, paired with clinical evidence of diabetes. Albuminuria reflects endothelial dysfunction and is associated with subclinical cardiac abnormalities such as left ventricular thickness, diastolic dysfunction, and elevated natriuretic peptide levels [30, 31]. These high-risk intermediate phenotypes observed with chronic kidney disease and diabetes likely contribute to the high risk of heart failure development when both conditions are present [32].

Obesity

The relationship between obesity, defined by a body mass index (BMI) of at least 30 kg/m^2, and heart failure is related to the effect of excess body mass on cardiac remodelling plus comorbid cardiovascular disease risk factors [33, 34]. A major driver of heart failure risk in obesity may be comorbid metabolic dysregulation. The elevated heart failure risk observed with higher measures of overall obesity, abdominal obesity, and fat mass appears to be related to comorbid risk factors [35, 36]. There is a suggestion that a metabolically healthy obese phenotype may not have an increased risk for developing heart failure. Compared with individuals with normal weight and metabolic syndrome, those with overweight and obesity but no metabolic syndrome had a lower risk of developing heart failure [37]. Similarly, among an older population, higher BMI levels were associated with the risk of heart failure, particularly in those with diabetes [38]. Taken together, there appears to be a synergistic effect between obesity and diabetes for the risk of developing heart failure.

Pathophysiology of heart failure in diabetes

Several pathophysiological mechanisms underlie the development of heart failure in diabetes, contributing to a vicious cycle (Figure 50.2). In diabetes, impaired glucose handling observed systemically follows a similar pattern in the heart. There is a shift in the substrate used to generate energy within the myocardium, with a relative increase in the oxidation of free fatty acids compared with glucose [39]. The alterations in cardiac metabolism are related to changes in the source of energy substrates and abnormal mitochondrial oxidative processes. Glucose uptake into the myocardium is reduced in diabetes due to a reduction in proteins that facilitate transport [40]. Additionally, fatty acid transport is enabled by the availability of transporters. The increased availability and free fatty acid oxidation further inhibit glucose oxidation. The shift in substrate utilization is necessary to meet the metabolic demands of the heart, but this process is maladaptive. To produce the same amount of adenosine triphosphate, oxidation of fatty acids versus glucose consumes more oxygen and increases myocardial oxygen consumption. Inefficient oxygen utilization leads to hypoxia and a vulnerable substrate at high risk for injury in the setting of ischaemia. The high burden of ischaemic heart disease in diabetes coupled with abnormal cardiac metabolism may partly explain the increased risk of heart failure observed in people with diabetes. Additionally, the delivery of fatty acids to the heart may exceed its oxidative needs, leading to an oversupply of lipids and lipotoxicity [41]. The deposition of lipids into the myocardium can lead to myocardial injury, inflammation, and adverse cardiac remodelling [42]. People with diabetes have greater triglyceride content within the myocardium than individuals without diabetes [43, 44]. This myocardial triglyceride content was associated with subclinical diastolic dysfunction, a known risk factor for heart failure development [45].

Hyperglycaemia can have impacts on heart failure risk both directly and indirectly. Elevated circulating glucose levels can lead to non-enzymatic glycation of lipids, proteins, and nucleic acids, resulting in advanced glycation end-products. Advanced glycation end-products can directly impact cardiac structure and function by modifying extracellular protein cross-linking, resulting in impaired relaxation and diastolic dysfunction [46]. The vascular system can also be affected by advanced glycation end-products, with resulting coronary atherosclerosis contributing to downstream heart failure risk. Hyperglycaemia also exacerbates neurohormonal activation, with upregulation of the renin–angiotensin system and greater adverse cardiac remodelling [42]. Therapies for managing HFrEF target this axis in people with and without diabetes. Finally, there is significant overlap in the epidemiology of diabetes with other cardiovascular risk factors, including hypertension, dyslipidaemia, chronic kidney disease, and obesity. Clustering of these cardiometabolic risk factors can increase the risk of heart failure through their impact on distinct and shared pathways.

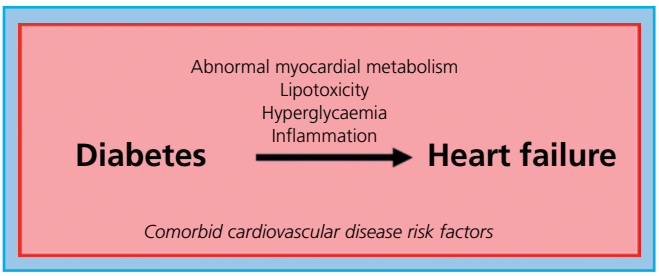

Figure 50.2 Proposed mechanisms underlying the pathophysiology of heart failure and diabetes.

Risk prediction and prevention of heart failure in diabetes

Diabetes management has until recently primarily focused on the prevention of atherosclerotic cardiovascular disease, with less attention dedicated to preventing heart failure [47]. Progress in reducing hospitalization for heart failure has lagged behind improvements observed in ischaemic heart disease [48]. Heart failure development occurs over a continuum from an at-risk stage identified by the presence of cardiovascular disease risk factors to subclinical abnormalities in cardiac structure and function, followed by eventual clinical heart failure. Prevention efforts have historically focused on targeting modifiable risk factors at earlier stages. Traditional risk factor management is critically important

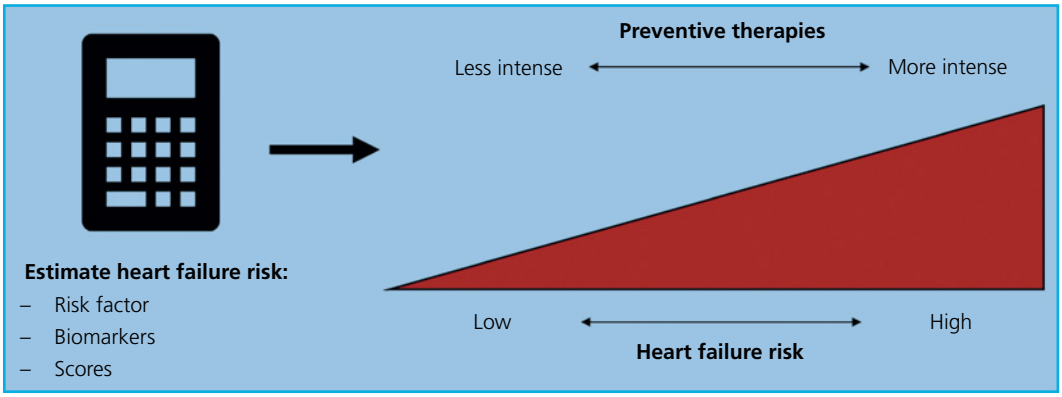

Figure 50.3 Preventive therapies can be targeted to people with diabetes and high risk for developing heart failure.

for cardiovascular disease prevention, but appears to be more beneficial for ischaemic heart disease than heart failure in the setting of diabetes [20]. Several tools have been developed to help guide the prescription of heart failure preventive therapies. Additionally, anti-diabetes therapies that effectively prevent heart failure are now available [49].

Heart failure risk assessment

A significant step in the primary prevention of heart failure is risk assessment. The estimated risk of heart failure can guide discussions and the selection of effective preventive therapies (Figure 50.3). People with diabetes and an elevated risk of heart failure are likely to derive the greatest absolute benefits from therapies.

Multiple risk scores are available to predict the risk of heart failure in the general population, with fewer specific to people with diabetes [50]. In an analysis from the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study, a risk score was developed to estimate incident heart failure risk among people with diabetes and established cardiovascular disease [51]. This heart failure risk score incorporated 12 variables, including demographics, medical history, medication use, and blood and urine laboratory measurements (Figure 50.4). This score had acceptable calibration and moderate discrimination (C-statistic 0.75) for predicting heart failure. The number of variables included in the risk score and the need for blood and urine studies may limit the usability of this tool, and external validation is needed. The WATCH-DM risk score was derived using machine learning to predict incident heart failure risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [52]. The integer-based WATCH-DM risk score had fair calibration and moderate discrimination (C-statistic 0.72) in an internal validation cohort and has demonstrated similar model performance in a clinical trial cohort and community-based cohorts of people with diabetes [53]. Additionally, the TIMI Risk Score for Heart Failure in Diabetes ($TRS\text{-}HF_{DM}$) was developed to predict the risk of heart failure among people with diabetes [54]. The placebo arm of the Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus–Thrombolysis In Myocardial Infarction (SAVOR-TIMI 53) trial was the derivation cohort, and the placebo arm of the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58) trial was the validation cohort. The $TRS\text{-}HF_{DM}$ risk score was calibrated and had good discrimination (C-index 0.81) for predicting heart failure. Unlike the WATCH-DM risk score and the heart failure risk score from PROactive, $TRS\text{-}HF_{DM}$ helps inform the risk of heart failure among people with and without a prior history of heart failure.

Biomarker screening may be a useful strategy for risk assessment and prevention of heart failure in diabetes [55]. In the STOP-HF trial, adults at increased risk for developing heart failure based on clinical history were randomly assigned to undergo screening with brain natriuretic peptide (BNP) measurement or usual care [56]. Participants who had BNP levels of at least 50 ng/l in the BNP screening arm subsequently underwent echocardiogram assessment and referral to a cardiovascular disease specialist. The odds of incident heart failure or left ventricular dysfunction were 45% lower in the BNP screening group than in usual care. Additional data from the NT-proBNP Selected PreventiOn of cardiac eveNts in a populaTion of dIabetic patients without A history of Cardiac disease (PONTIAC) trial suggests that individuals with diabetes and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels of at least 125 ng/l benefit from rapid uptitration of neurohormonal blocking therapies and referral to a cardiovascular disease specialist [57]. Intensified treatment in this population identified by NT-proBNP levels reduced the risk of cardiac events by 65%.

Heart failure risk scores incorporating biomarkers, including natriuretic peptides, have been developed. A biomarker score was developed in a pooled cohort study of community-dwelling adults that included high-sensitivity cardiac troponin T (hs-cTnT), NT-proBNP, high-sensitivity C-reactive protein, and left ventricular hypertrophy based on electrocardiogram [58]. In a population with diabetes, the biomarker risk score demonstrated adequate calibration and good discrimination (C-statistic 0.74) for predicting the five-year risk of developing heart failure. Finally, the TIMI Biomarker Score for Heart Failure in Diabetes was derived in the SAVOR-TIMI 53 trial. It incorporated a combination of blood-based biomarkers (hs-cTnT and NT-proBNP) and a prior history of heart failure to estimate the risk of hospitalization for heart failure among individuals with diabetes with and without prior history of heart failure [59]. This biomarker-based risk score demonstrated adequate calibration and good discrimination (C-index 0.87) for predicting heart failure risk.

Preventive therapies for heart failure

Healthy lifestyle

A healthy lifestyle focused on physical activity and weight loss in people with overweight or obesity is recommended to prevent heart failure [60]. Epidemiological studies have shown that higher BMI and lower physical activity and cardiorespiratory fitness are associated with a higher risk of heart failure [61–65]. The Look AHEAD (Action for Health in Diabetes) trial was a randomized controlled trial that evaluated the effect of an intensive lifestyle intervention focused on

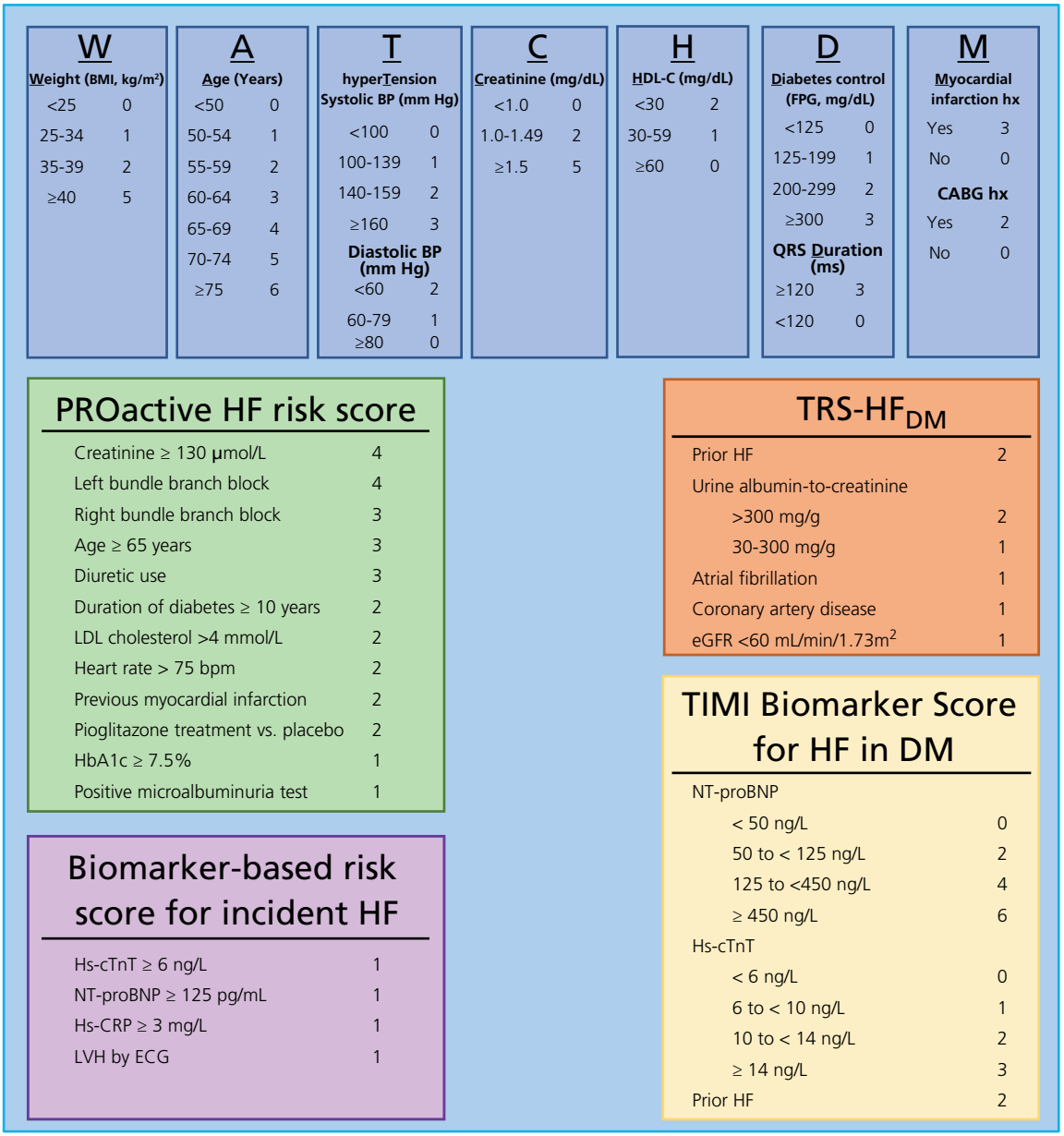

Figure 50.4 Diabetes-specific scores to estimate heart failure risk.

weight loss on cardiovascular outcomes among adults with diabetes and overweight or obesity [66]. In this trial, the intensive lifestyle intervention led to weight loss and fitness improvement at one year, but these benefits were not sustained over follow-up. During follow-up, the intensive lifestyle intervention did not reduce the risk of a composite cardiovascular disease endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for angina. Additionally, the rate of heart failure was similar between participants randomized to the intensive lifestyle intervention and placebo groups [36]. A potential explanation for the null effect of the intensive lifestyle intervention on cardiovascular disease and heart failure outcomes is the lack of sustained improvements in weight and fitness. *Post hoc* analyses demonstrated that reduction in BMI was associated with a significantly lower risk of heart failure [36]. Similarly, reduction in other body composition measures such as waist circumference and fat mass were also associated with a significantly lower risk of heart failure [35]. While the risk of cardiovascular disease was not reduced in this trial, the intensive lifestyle intervention improved several clinically relevant cardiovascular risk factors.

Blood pressure management

Hypertension is an important risk factor for heart failure for several reasons:

- Hypertension is common and affects almost half of all adults in the USA [67].
- Heart failure risk is more than doubled in people with hypertension than in those with normal blood pressure [68].
- Hypertension is a modifiable risk factor for cardiovascular disease.

The beneficial effects of blood pressure lowering are greater for reducing heart failure risk compared with other cardiovascular diseases [69]. In the general population, for every 10 mmHg reduction in

Table 50.1 Heart failure prevalence and outcomes in cardiovascular outcome trials of incretin-based therapies and sodium–glucose cotransporter 2 inhibitors.

Trial	Year	Drug	Number	History of heart failure (%)	Heart failure Hazard ratio (95% confidence interval)
Dipeptidyl peptidase 4 (DPP-4) inhibitors					
EXAMINE [73, 74]	2013	Alogliptin	5380	28	1.07 (0.79 to 1.46)
SAVOR-TIMI 53 [75]	2013	Saxagliptin	16 492	13	1.27 (1.07 to 1.51)
TECOS [76]	2015	Sitagliptin	14 671	18	1.00 (0.83 to 1.20)
CARMELINA [77]	2019	Linagliptin	6991	27	0.90 (0.74 to 1.08)
CAROLINA [78]	2019	Linagliptin	6042	4–5	1.21 (0.92 to 1.59)
Glucagon-like peptide 1 (GLP-1) receptor agonists					
ELIXA [79]	2015	Lixisenatide	6068	22	0.96 (0.75 to 1.23)
LEADER [80]	2016	Liraglutide	9340	18	0.87 (0.73 to 1.05)
SUSTAIN-6 [81]	2016	Semaglutide (SC)	3297	24	1.11 (0.77 to 1.61)
EXSCEL [82]	2017	Exenatide	14 752	16	0.94 (0.78 to 1.13)
HARMONY OUTCOMES [83, 156]	2018	Albiglutide	9463	20	0.71 (0.53 to 0.94)
REWIND [84]	2019	Dulaglutide	9901	9	0.93 (0.77 to 1.12)
PIONEER 6 [85]	2019	Semaglutide (oral)	3183	12	0.86 (0.48 to 1.55)
AMPLITUDE-O [86]	2021	Efpeglenatide	4076	18	0.61 (0.38 to 0.98)
Sodium glucose cotransporter 2 (SGLT-2) inhibitors					
EMPA-REG OUTCOME [72]	2015	Empagliflozin	7020	10	0.65 (0.50 to 0.85)
CANVAS [87]	2017	Canagliflozin	10 142	14	0.67 (0.52 to 0.87)
DECLARE-TIMI 58 [88]	2019	Dapagliflozin	17 160	10	0.73 (0.61 to 0.88)
CREDENCE [89]	2019	Canagliflozin	4401	15	0.61 (0.47 to 0.80)
VERTIS CV [90]	2021	Ertugliflozin	8246	24	0.70 (0.54 to 0.90)

systolic blood pressure, the risk of cardiovascular disease and heart failure is lower by 20% and 28%, respectively. However, diabetes appears to modify the association between systolic blood pressure and cardiovascular disease. The relative risk reduction in cardiovascular disease observed with blood pressure management was lower for people with diabetes (relative risk [RR] 0.88; 95% confidence interval [CI] 0.82 to 0.94) compared with those without diabetes (RR 0.75; 95% CI 0.70 to 0.80). Similarly, blood pressure management appears to have less of an effect on reducing heart failure risk in people with diabetes (RR 0.84; 95% CI 0.72 to 0.98) compared with those without diabetes (RR 0.75; 95% CI 0.65 to 0.87), although there was no significant interaction. In the ACCORD blood pressure trial, 4733 people with diabetes and an elevated risk for cardiovascular disease were randomly assigned to a systolic blood pressure target of <120 mmHg or <140 mmHg [70]. Intensive blood pressure management did not reduce the risk of a composite atherosclerotic cardiovascular disease endpoint or heart failure. In a meta-analysis of 24 444 people with diabetes, intensive blood pressure lowering was associated with a lower risk of all-cause death, myocardial infarction, and stroke, but not heart failure [71]. In 2022, the American Diabetes Association (ADA) recommended blood pressure targets based on the risk of future cardiovascular disease events [47]. A blood pressure target of <140/90 mmHg was recommended for individuals with diabetes and a 10-year estimated risk of atherosclerotic cardiovascular disease <15%. In contrast, a blood pressure target <130/90 mmHg was recommended for individuals with diabetes and either a history of cardiovascular disease or a 10-year estimated risk of atherosclerotic cardiovascular disease of at least 15%.

Sodium–glucose cotransporter 2 inhibitors

The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG) OUTCOME trial evaluated the cardiovascular safety of empagliflozin, a sodium–glucose cotransporter 2 (SGLT-2) inhibitor, among 7020 people with diabetes and established cardiovascular disease [72]. People randomized to empagliflozin treatment received once-daily empagliflozin at a dose of 10 or 25 mg, and these doses were pooled in the primary analysis of the trial. After a median observed follow-up of three years, empagliflozin reduced the risk of a composite of cardiovascular death, nonfatal myocardial infarction, or non-fatal stroke by 14%. The EMPA-REG OUTCOME trial was the first study to demonstrate a significant reduction in cardiovascular disease risk with an antidiabetes medication in the modern era. The beneficial effects of empagliflozin in the composite atherosclerotic cardiovascular disease endpoint were significant, but perhaps more remarkable was the 35% reduction in heart failure hospitalization. The beneficial effects of the SGLT-2 inhibitor class of medications on the risk of heart failure hospitalization appear to be a class effect [49]. Canagliflozin, dapagliflozin, and ertugliflozin also demonstrated marked reductions in heart failure hospitalization among people with diabetes (Table 50.1) [87–90]. Due to the enrolment of few people with heart failure in these cardiovascular outcome trials, several SGLT-2 inhibitors are considered effective therapies to prevent heart failure. As discussed later, the cardiovascular effects of SGLT-2 inhibitors were studied further in prevalent heart failure. This class of medications has evolved from a glucose-lowering therapy to a therapeutic class that can be used to prevent and manage heart failure. The mechanism of benefit of SGLT-2 inhibitors is not well established, but is likely related to several complementary effects. A summary of the pleiotropic effects of SGLT-2 inhibitors that likely contribute to lowering heart failure risk is shown in Figure 50.5 [91].

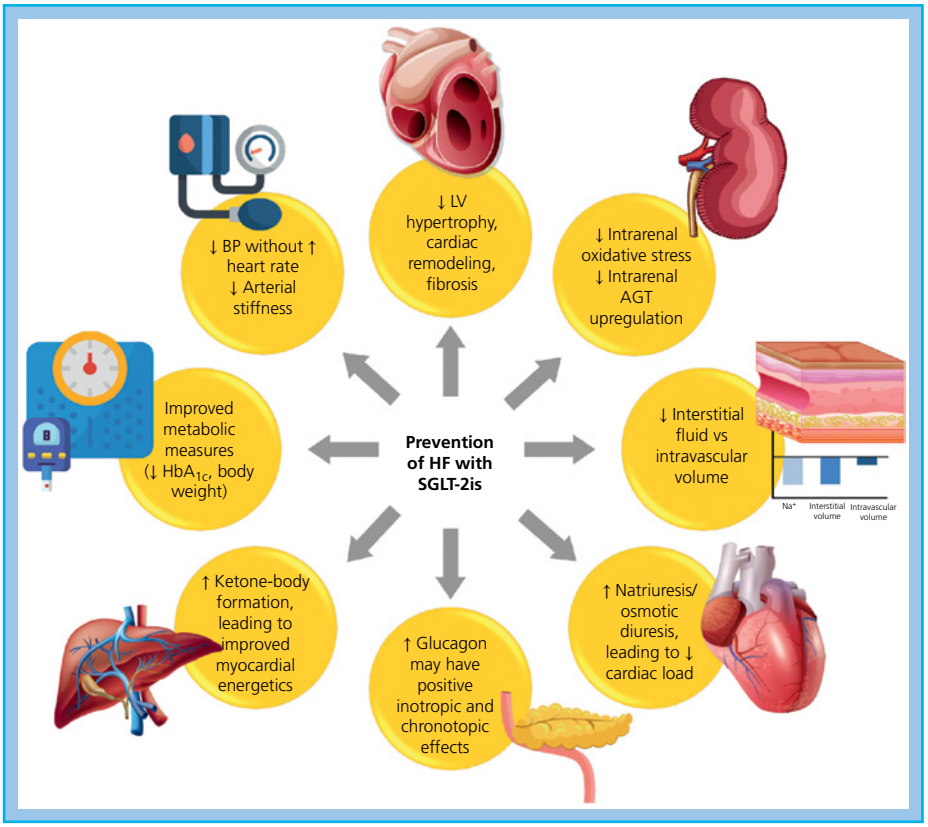

Figure 50.5 Summary of the pleiotropic effects of sodium–glucose cotransporter 2 inhibitors (SGLT-2is). AGT, angiotensinogen; BP, blood pressure; HF, heart failure; LV, left ventricular. Source: Reproduced with permission from John Wiley and Sons; Butler et al. 2020 [91].

Outcomes in people with comorbid diabetes and heart failure

The prevalence of comorbid diabetes is common among people with heart failure and is associated with an excess risk of adverse outcomes [92, 93]. Among people with heart failure, those with diabetes more commonly had New York Heart Association class III or IV symptoms and lower six-minute walk distance than those without diabetes [94]. Additionally, prevalent diabetes is associated with a 46% higher risk of unfavourable quality of life based on the Kansas City Cardiomyopathy Questionnaire [95]. After a diagnosis of heart failure, diabetes is one of the strongest predictors of hospitalization after accounting for other cardiovascular disease risk factors [96]. The risk of hospitalization and mortality in heart failure is also largely influenced by diabetes status. All-cause, cardiovascular, and heart failure hospitalizations and death were all higher among people who had heart failure with versus without diabetes [97]. After accounting for differences in cardiovascular risk factors, the risk of death is 28% higher among people with diabetes compared to those without diabetes [93]. The prevalence of comorbid diabetes and heart failure is similar across heart failure subtypes, but the prognosis differs [18]. In a *post hoc* analysis of the Candesartan in Heart failure—Assessment of Reduction in Mortality and morbidity (CHARM) trial, diabetes-associated risk of cardiovascular death or heart failure hospitalization was higher among people with HFpEF compared with HFrEF (hazard ratio [HR] 2.0; 95% CI 1.70 to 2.36; vs 1.60; 95% CI 1.44 to 1.77, respectively) [97]. In contrast, diabetes was associated with similar excess risk of death in HFrEF and HFpEF (HR 1.55; 95% CI 1.38 to 1.74; vs 1.84; 95% CI 1.51 to 2.26, respectively).

Treatment considerations for heart failure and diabetes

Diabetes affects heart failure development through several underlying mechanisms, with direct and indirect effects on the myocardium, and may modify the response to heart failure therapies. Due to the increased risk of adverse outcomes with comorbid diabetes and heart failure and the broad impact of therapies, management considerations for each disease in the presence of the other will be highlighted. Large, randomized controlled trials of therapies for HFrEF and left ventricular systolic dysfunction enrolled a large proportion of participants with diabetes and provided evidence regarding therapeutic response across diabetes strata (Table 50.2).

Heart failure with reduced ejection fraction therapies among people with diabetes

Renin–angiotensin system inhibition

Inhibition of the renin–angiotensin system with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and angiotensin receptor neprilysin inhibitor (ARNI) reduced the risk of cardiovascular disease in HFrEF across the

Table 50.2 Prevalence of type 2 diabetes in selected trials enrolling people with heart failure with reduced ejection fraction or left ventricular systolic dysfunction.

Trial	Year	Drug/device	Study population	N	Diabetes %
Angiotensin-converting enzyme (ACE) inhibitor					
CONSENSUS [98]	1987	Enalapril	HFrEF	253	21–24
SOLVD-Treatment [99]	1991	Enalapril	HFrEF	2569	25–27
SAVE [100]	1992	Captopril	LVSD post-MI	2231	21–23
TRACE [101]	1995	Trandolapril	LVSD post-MI	1749	13–14
Angiotensin receptor blocker					
Val-HeFT [102]	2001	Valsartan	HFrEF	5010	25–26
VALIANT [103]	2003	Valsartan	HFrEF, LVSD post-MI	14 703	23–24
CHARM [104]	2004	Candesartan	HFrEF	4576	29
Angiotensin receptor neprilysin inhibitor					
PARADIGM-HF [105]	2014	Sacubitril-valsartan	HFrEF	8442	35
β-blocker					
MERIT-HF [106]	1999	Metoprolol succinate	HFrEF	3991	24–25
CIBIS-II [107, 108]	1999	Bisoprolol	HFrEF	2647	12
COPERNICUS [162]	2001	Carvedilol	HFrEF	2289	26
Mineralocorticoid receptor antagonist					
RALES [109]	1999	Spironolactone	HFrEF	1663	22
EPHESUS [110]	2003	Eplerenone	HFrEF, LVSD post-MI	6632	32
EMPHASIS-HF [111]	2011	Eplerenone	HFrEF	2737	29–34
Sodium–glucose cotransporter 2 (SGLT-2)inhibitor					
DAPA-HF [112]	2019	Dapagliflozin	HFrEF	4744	42
EMPEROR-reduced [113]	2020	Empagliflozin	HFrEF	3730	50
SOLOIST-WHF [114]	2021	Sotagliflozin	HFrEF, HFpEF	1222	100
Implantable cardioverter-defibrillator					
MADIT-II [115, 116]	2002	ICD	LVSD post-MI	1232	40
SCD-HeFT [117, 118]	2005	ICD	HFrEF	2521	32
Cardiac resynchronization therapy					
COMPANION [119, 120]	2004	CRT	HFrEF	1520	41
CARE-HF [121, 122]	2005	CRT	HFrEF	813	25
MADIT-CRT [123, 124]	2009	CRT	HFrEF	1820	30
RAFT [125]	2010	CRT	HFrEF	1798	33–35

HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction.

diabetes strata. In a meta-analysis, ACE inhibitors demonstrated 16% and 15% RR reduction in death among people with (n = 2398) and without diabetes (n = 10 188), respectively [126]. Given the higher rate of mortality observed with diabetes, the absolute benefit of ACE inhibitors is expected to be large in this population with HFrEF. A similar pattern of benefits was observed for an ARB. In the CHARM programme, the beneficial effect of candesartan in heart failure was comparable among people irrespective of diabetes status [97]. The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial evaluated the effects of ARNI with sacubitril-valsartan on morbidity and mortality among participants with HFrEF, of whom 35% had diabetes [105]. Diabetes status did not modify the benefit of sacubitril-valsartan for reducing cardiovascular disease. This trial enrolled a larger proportion of participants with diabetes compared with ACE inhibitor and ARB trials in HFrEF (Table 50.2). All three classes of agents appear to have glucose-lowering effects. Among people with HFrEF or left ventricular dysfunction, enalapril reduced the incidence of diabetes [127]. Similar findings were observed for candesartan in heart failure [128]. However, the effect of enalapril and candesartan on glucose levels among people with comorbid diabetes and HFrEF is not well-established. In comorbid HFrEF and diabetes, sacubitril-valsartan reduced HbA_{1c} over three years, insulin use, and oral anti-diabetes medication use on follow-up [129]. Taken together, the renin–angiotensin system may affect both HFrEF and glucose homeostasis, and inhibition of this shared pathway may improve both comorbid conditions.

β-blockers

β-blockers reduce the risk of adverse outcomes in people with HFrEF with or without diabetes. A meta-analysis of three clinical trials of β-blockers (bisoprolol, carvedilol, and metoprolol succinate) included 1883 people with diabetes and 7042 people without diabetes and revealed a similar 23–35% reduction in death across diabetes strata [126]. However, there are several concerns regarding the adverse metabolic effects of β-blockers. Theoretically, β-blockers may decrease recognition of hypoglycaemia by slowing the heart rate and blunting tremors [130]. In the setting of hypoglycaemia, compensatory hepatic glucose production may be attenuated by blockade of the β_2-receptor. β-blockers may also be associated with

impaired glucose tolerance or diabetes. Epidemiological evidence from the Atherosclerosis Risk in Communities (ARIC) study demonstrated a 28% higher risk of developing diabetes using β-blockers [131]. These findings are supported by separate studies showing that selective (atenolol, metoprolol) and non-selective β-blockers (propranolol) reduce glucose uptake [132, 133]. In contrast, blockade of the α-receptor can promote insulin sensitivity and enhance glucose uptake [134]. Carvedilol, an α- and β-adrenergic blocker, reduces HbA_{1c} and the incidence of diabetes in people with HFrEF [135, 136]. These favourable metabolic effects of carvedilol were not observed with metoprolol or bisoprolol and may be related to the vasodilatory properties of this medication [137].

Mineralocorticoid receptor antagonists

Mineralocorticoid receptor antagonists reduce morbidity and mortality in HFrEF [109–111]. Randomized clinical trials of eplerenone demonstrated consistent benefits among people with and without diabetes [110, 111]. In the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial, eplerenone did not increase the rate of new-onset diabetes compared with placebo [138]. In contrast, spironolactone increases HbA_{1c} and appears to have worse metabolic effects than eplerenone [139, 140]. Taken together, eplerenone may have a more favourable metabolic profile compared with spironolactone in HFrEF.

Sodium–glucose cotransporter 2 inhibitors

As discussed earlier, SGLT-2 inhibitors were originally developed to lower glucose, but were serendipitously found to reduce the risk of cardiovascular disease. One of the most consistent findings of the SGLT-2 inhibitor class was their effect on reducing the risk of heart failure hospitalization [72, 87, 88, 90]. The majority of people enrolled in SGLT-2 inhibitor cardiovascular outcome trials were free of heart failure, suggesting that SGLT-2 inhibitors prevented the development of heart failure (Table 50.1). The DECLARE-TIMI 58 trial was the largest diabetes cardiovascular outcome trial, which enrolled 17 160 participants with type 2 diabetes and evaluated the safety of dapagliflozin [88]. In a secondary analysis, approximately 12% of participants had a history of heart failure at baseline, and this subgroup benefited the most from dapagliflozin, thus suggesting that SGLT-2 inhibitors may be beneficial among people with prevalent heart failure [141]. As such, SGLT-2 inhibitors were subsequently evaluated in clinical trials of people with a history of heart failure.

Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) was the first phase 3 clinical trial to evaluate the effects of an SGLT-2 inhibitor among people with HFrEF with and without diabetes [112]. Among 4744 people with HFrEF, dapagliflozin reduced the composite endpoint of cardiovascular death or worsening heart failure by 26%. These beneficial effects of dapagliflozin were similar for people with and without diabetes [142]. Compared with people randomized to placebo, those in the dapagliflozin group had lower rates of hospitalization for heart failure (9.7% vs 13.4%) and death from cardiovascular causes (9.6% vs 11.5%). A similar pattern of benefit was observed with empagliflozin among people with HFrEF in the EMPagliflozin outcomE tRial in patients with chrOnic heaRt failure with Reduced ejection fraction (EMPEROR-Reduced) trial [113]. Compared with placebo, empagliflozin reduced the primary composite endpoint of hospitalization for heart failure or cardiovascular death by 25%, with similar benefits across diabetes strata [143]. The proportion of people who died from cardiovascular causes was not different across the two treatment arms [144]. The DAPA-HF and EMPEROR-Reduced trials enrolled people with clinically stable HFrEF in an outpatient setting. In contrast, the Effect of Sotagliflozin on Cardiovascular Events in Participants with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial enrolled people with diabetes and heart failure across the spectrum of left ventricular ejection fraction who were recently hospitalized for heart failure and evaluated the effects of sotagliflozin, an SGLT-1 and SGLT-2 inhibitor, on cardiovascular outcomes [114]. In the study, 1222 people were randomized to receive either sotagliflozin or placebo prior to or within three days of discharge. Due to funding issues, the SOLOIST-WHF trial was terminated prior to enrolling the planned number of participants. The primary outcome was modified to increase the power of the study, and study outcomes were based on investigator-reported events rather than standard adjudication. In the context of these major limitations, sotagliflozin reduced the risk of a total composite number of cardiovascular deaths and heart failure hospitalizations and urgent visits by 33%.

Implantable cardioverter-defibrillators

Implantable cardioverter-defibrillators (ICDs) are used in HFrEF to reduce mortality by preventing sudden cardiac death. The Multicenter Autonomic Defibrillator Implantation Trial II (MADIT-II) enrolled people with myocardial infarction and reduced left ventricular systolic function and found that ICDs reduced mortality risk by 31% [115]. The beneficial effect of ICDs on mortality was similar across diabetes strata [116]. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) was designed to evaluate whether ICDs would prevent death among people with HFrEF [117]. ICDs reduced the risk of death in SCD-HeFT, with no difference in results according to ischaemic aetiology. In the subgroup analysis by diabetes status, the beneficial effects of ICD therapy varied according to diabetes status. ICDs reduced the risk of death among people without diabetes but not those with diabetes [118]. Potential explanations for the lack of benefit of ICDs in people with versus without diabetes may be related to less effective ICD therapy or higher risk of death from causes other than sudden cardiac death in this population. In a separate study, inappropriate ICD therapy was found to be less common among participants with diabetes [145]. A pooled analysis of several studies suggested that ICD therapy may be less beneficial in people with a high burden of comorbidities [146]. Taken together, the risk–benefit profile of each person with diabetes should be considered when considering ICD therapy in this high-risk group.

Cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) reduces intraventricular conduction delays among people with HFrEF and cardiac desynchrony. In the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial, 1520 people with HFrEF (New York Heart Association class III or IV) and a QRS interval ≥120 ms were randomly assigned to either optimal medical therapy or optimal medical therapy plus CRT with and without an ICD [119]. CRT reduced the risk of death or hospitalization for any cause, with consistent benefits among people with and without diabetes [120]. The effect of CRT on cardiovascular events was not modified by diabetes status. Similar findings were observed in the CArdiac REsynchronisation in Heart Failure (CARE-HF) trial with moderate or severe HFrEF [121, 122]. The Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) and Resynchronization–defibrillation for Ambulatory heart Failure Trial (RAFT) investigated the effects of CRT among

people with less severe HFrEF and demonstrated improvements in cardiovascular outcomes that were similar among people with and without diabetes [123–125].

Heart failure with preserved ejection fraction therapies among people with diabetes

Efforts to improve cardiovascular outcomes in HFpEF with pharmacological therapies have historically been met with challenges, due in part to the heterogeneity of the clinical syndrome. Inhibition of the renin–angiotensin system, β-blockers, mineralocorticoid receptor antagonists, and other HFrEF therapies have not yielded robust benefits in clinical trials of HFpEF. Preliminary evidence from the SOLOIST-WHF trial suggested that inhibition of SGLT-1 and SGLT-2 with sotagliflozin reduced cardiovascular death and heart failure hospitalizations and urgent visits, with beneficial effects in heart failure across the spectrum of left ventricular ejection fraction extending to the preserved range [114]. However, the SOLOIST-WHF trial should be interpreted in the context of the major limitations noted earlier in this chapter. The EMPagliflozin outcomE tRial in patients with chrOnic heaRt failure with Preserved ejection fraction (EMPEROR-Preserved) trial enrolled 5998 people with HFpEF, of which approximately one-half had diabetes, to receive the SGLT-2 inhibitor empagliflozin or placebo [147]. Empagliflozin reduced cardiovascular death or heart failure hospitalization by 21% compared with placebo. The effect of empagliflozin on cardiovascular disease events in HFpEF was consistent across diabetes strata, with a 21% and 22% relative risk reduction in the primary endpoint among participants with and without diabetes, respectively.

Anti-diabetes medications among people with or at high risk for developing heart failure

Thiazolidinediones

The relationship between certain anti-diabetes medications and heart failure risk is well-established. Thiazolidinediones cause peripheral oedema and can provoke heart failure, leading to recommendations against using this class of medications in people with heart failure [148]. In the PROactive study, 5238 people with diabetes and established cardiovascular disease were randomised to pioglitazone or placebo [149]. After ~3 years of follow-up, pioglitazone reduced the risk of a composite atherosclerotic cardiovascular disease endpoint non-significantly, but increased the risk of heart failure (11% vs 8%). The concerns for heart failure risk with thiazolidinediones were further bolstered by an analysis of clinical trial data from five studies of muraglitazar that demonstrated an increased risk of cardiovascular disease, including heart failure [150]. After concerns were raised regarding the cardiovascular safety of another thiazolidinedione, rosiglitazone [151], an unplanned interim analysis of a cardiovascular outcome trial evaluating rosiglitazone was performed and revealed increased heart failure risk [152]. The cardiovascular safety concerns for anti-diabetes medications such as thiazolidinediones led the US Food and Drug Administration (FDA) to issue guidance in 2008 recommending new anti-diabetes medications to demonstrate cardiovascular safety in cardiovascular outcome trials [6].

Dipeptidyl peptidase 4 inhibitors

Incretin-based therapies, including dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists, have been evaluated in several diabetes cardiovascular outcome trials. The SAVOR-TIMI 53 trial [75] was one of the first diabetes cardiovascular outcome trials published after the FDA modified its approval process for anti-diabetes medications. In this trial, 16 492 people with diabetes and established or at high risk for developing cardiovascular disease were randomly assigned to receive the DPP inhibitor saxagliptin or placebo. Saxagliptin did not significantly increase the risk of the composite atherosclerotic cardiovascular disease endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal ischaemic stroke. However, the risk of heart failure hospitalization was higher among people who received saxagliptin compared with placebo. Excess risk of hospitalization for heart failure was apparent as early as six months after randomization and persisted during follow-up [153]. A similar pattern of cardiovascular effects was observed for another DPP-4 inhibitor, alogliptin.

In the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial, 5380 people with diabetes who had a recent acute coronary syndrome were randomized to treatment with alogliptin or placebo [73]. There were no major differences in atherosclerotic cardiovascular disease between the groups. Due to the elevated heart failure risk observed with saxagliptin, a separate analysis of the EXAMINE trial was performed to evaluate whether alogliptin increased the risk of heart failure [74]. A summary of the DPP-4 inhibitor trials, including heart failure prevalence and risk of heart failure, is shown in Table 50.1. More than one-quarter of participants enrolled in EXAMINE had heart failure at baseline. The absolute rate of heart failure hospitalization was higher, although not statistically significant, among people randomized to treatment with alogliptin versus placebo. Among people with no history of heart failure, alogliptin increased the risk of hospitalization for heart failure by 76%. However, the excess heart failure risk observed with saxagliptin and alogliptin is not a class effect. In the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) trial, among 14 671 people with diabetes and established cardiovascular disease, sitagliptin did not affect the risk of heart failure hospitalization [76]. Similarly, in two cardiovascular outcome trials with linagliptin, the DPP-4 inhibitor did not meaningfully modify heart failure risk among people with diabetes compared with placebo or glimepiride [77, 78].

The DPP-4 inhibitor cardiovascular outcome trials described here included a small proportion of participants enrolled with prevalent heart failure, limiting the safety assessment of this class of medication in this population (Table 50.1). The Vildagliptin in Ventricular Dysfunction Diabetes (VIVIDD) trial enrolled 254 people with HFrEF and diabetes and evaluated the safety of the DPP-4 inhibitor vildagliptin on left ventricular function [154]. Based on the trial's primary objective, vildagliptin appeared safe for its effects on left ventricular ejection fraction. A similar increase in left ventricular ejection fraction was observed in people who received vildagliptin and placebo. However, people who received vildagliptin had an increase in left ventricular end-diastolic volume, which is correlated with elevated mortality risk [155]. These findings paired with the trend towards higher death in the vildagliptin versus placebo group suggest further study is warranted regarding the safety of this agent in HFrEF.

Glucagon-like peptide 1 receptor agonists

Several GLP-1 receptor agonists have demonstrated consistent benefits in lowering the risk of atherosclerotic cardiovascular disease [156]. However, the effects of this drug class on heart failure outcomes have been less consistent (Table 50.1). Most GLP-1 receptor agonists demonstrated neutral effects on heart failure in

cardiovascular outcome trials, except for albiglutide and efpglenatide. In the Harmony Outcomes trial, 9463 participants with diabetes were randomly assigned to receive albiglutide or placebo [83]. Participants randomized to receive albiglutide had a 29% lower risk of heart failure hospitalization compared with placebo [156]. The Effect of Efpeglenatide on Cardiovascular Outcomes (AMPLITUDE-O) trial, which enrolled 4076 people with diabetes, similarly demonstrated a 39% reduction in the risk of heart failure hospitalization with efpglenatide [86]. A meta-analysis pooled data from eight GLP-1 receptor agonist cardiovascular outcome trials and found an 11% relative risk reduction in heart failure hospitalization with this class of medications [156].

The mechanisms underlying the beneficial effects of GLP-1 receptor agonists on heart failure are not well-established [157, 158]. A potential explanation may be related to the effect of GLP-1 receptor agonists in preventing myocardial infarction, a major risk factor for heart failure. Compared with other agents in the class, albiglutide and efpglenatide demonstrated the most considerable reductions in risk of myocardial infarction in their respective cardiovascular outcome trials.

Most people enrolled in the Harmony Outcomes trial did not have a prior history of heart failure (80%), suggesting that albiglutide was effective in preventing heart failure, but its effects on prevalent heart failure were less clear [83]. The cardiovascular effects of albiglutide were evaluated in a trial of 82 people with HFrEF and no history of diabetes [159]. Albiglutide mainly had neutral effects in HFrEF, with no meaningful differences compared with placebo on left ventricular ejection fraction and myocardial glucose uptake. A similar neutral effect on left ventricular ejection fraction was observed among people with HFrEF with and without diabetes who were randomly assigned to receive liraglutide or placebo in the Effect of Liraglutide on Left Ventricular Function in Chronic Heart Failure Patients with and without Type 2 Diabetes Mellitus (LIVE) trial [160]. However, there were some concerns regarding the safety of liraglutide in HFrEF. People who received liraglutide had an increase in heart rate and the rate of serious adverse cardiac events compared with placebo. These safety concerns of GLP-1 receptor agonists in HFrEF were further supported by evidence from the Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) trial, which evaluated the effects of liraglutide among 300 high-risk people with HFrEF with and without diabetes [161]. The rate of rehospitalization for heart failure was higher, although not statistically significant, among people randomized to receive liraglutide versus placebo. Despite the safety concerns for GLP-1 receptor agonist use in HFrEF, there may be a role for this class of agents in HFpEF. The pathophysiology of heart failure subtypes is distinct, and the non-cardiac effects of GLP-1 receptor agonists, specifically weight loss, may be beneficial in HFpEF and require further study [157].

Sodium glucose cotransporter 2 inhibitors

Several large cardiovascular outcome trials examining the effects of SGLT-2 inhibitors have been published in the last five years. SGLT-2 inhibitors are now recommended for the prevention and management of heart failure [60]. Among people with diabetes who are at increased risk for developing heart failure, SGLT-2 inhibitors are recommended to prevent heart failure. Additionally, SGLT-2 inhibitors are recommended in the management of both heart failure subtypes.

Metformin

Metformin has historically been recommended as the first-line agent for managing hyperglycaemia in diabetes [162, 163]. In the heart failure setting, there were concerns early on regarding lactic acidosis associated with metformin, limiting its use. However, the initial contraindication to metformin use in heart failure was removed as more data emerged. It should be noted that there are limited randomized controlled trial data available examining metformin use in people with heart failure.

Sulfonylureas

Sulfonylureas are commonly used, but there are no placebo-controlled trials evaluating the cardiovascular safety of this class. Glimepiride, a sulfonylurea, was evaluated in the randomized, active-controlled Cardiovascular Outcome Study of Linagliptin vs Glimepiride in Type 2 Diabetes (CAROLINA) trial [78]. In this trial, 6991 people with diabetes were randomly assigned to receive glimepiride or linagliptin. The rate of heart failure hospitalization was not significantly different among people who received linagliptin (3.7%) and glimepiride (3.1%).

Insulin

The effect of different types of insulin on cardiovascular outcomes has been evaluated in two trials. The Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial randomly assigned 12 537 people with pre-diabetes or diabetes plus cardiovascular risk factors to receive insulin glargine or standard of care [164]. People randomized to receive glargine targeted a fasting plasma glucose of 95 mg/dl (5.3 mmol/l) or less. After six years of follow-up, there was no significant difference in the risk of heart failure hospitalization between the two groups. Heart failure hospitalization occurred in 4.9% of people in the glargine group and 5.5% of people in the standard care group. A separate cardiovascular outcome trial was performed to evaluate the cardiovascular safety of insulin degludec, an ultra-long-acting basal insulin, compared with insulin glargine [165]. In the Trial Comparing Cardiovascular Safety of Insulin Degludec vs Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE), among 6509 people with diabetes and high risk for cardiovascular disease, there was no difference in heart failure risk among people randomized to the insulin degludec or glargine groups [166].

Overall, the response to most heart failure therapies is not modified by diabetes status and management of both HFrEF and HFpEF is similar for people with and without diabetes. In contrast, several factors should be considered in the use of anti-diabetes medications in people who are at elevated risk for developing heart failure or who have heart failure.

Conclusion

The burden of diabetes is growing in the community, highlighting the need for greater focus on preventive efforts to reduce the risk of downstream cardiovascular complications such as heart failure and for optimal management of people with coexisting diabetes and heart failure. To this end, substantial therapeutic advances have been made in the past decade with the use of SGLT-2 inhibitors for prevention and management of heart failure. The future challenges pertain to the development of efficient implementation strategies to identify and treat the people with diabetes who will most benefit from effective but expensive therapies in the real world.

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51 Cerebrovascular Disease and Diabetes

Colum F. Amory[1], Jesse Weinberger[2], and Travis S. Smith[1]

[1] Albany Medical College, Albany, NY, USA

[2] Mount Sinai School of Medicine, New York, NY, USA

Key points

- Diabetes is a strong and independent risk factor for ischaemic cerebrovascular disease with a relative risk of ~2.
- Ischaemic stroke in people with diabetes has worse outcomes, including a higher rate of mortality, than in people without diabetes.
- Although transient ischaemic attacks (TIAs) appear to occur less frequently in individuals with diabetes, those who experience a TIA are more likely to go on to have a completed stroke in the immediate period following.
- Individuals with diabetes are predisposed to vascular events, including stroke, for several reasons, such as premature atherosclerosis, reduced response to nitric oxide, and a general state of hypercoagulability.
- Prevention of stroke in people with diabetes is best accomplished through aggressive management of coexisting hypertension and hyperlipidaemia, in addition to health behaviour modifications.
- Reduction of glycated haemoglobin as a proxy for good glycaemic management is likely associated with a reduction in macrovascular events.
- Aggressive management of hyperglycaemia in the acute stroke period may improve outcomes.

Epidemiology of stroke in general

Cerebrovascular disease is a leading cause of morbidity and mortality. It is a highly prevalent disease, with ~795 000 strokes occurring each year in the USA. Of these, 610 000 are first-time events and 185 000 are recurrent [1]. Stroke prevalence is 2.6% in people over 20 years of age. While the incidence and mortality rates of stroke have declined over the past several decades, it remains the fifth leading cause of death in the USA, following heart disease, all forms of cancer, trauma, and chronic lower respiratory disease [2]. Thus, a woman is nearly twice as likely to die from a stroke as she is from breast cancer, and 10% more likely than to die from lung cancer [3]. Furthermore, it is the number one reason listed for discharge diagnosis for people discharged from hospitals to chronic care facilities. In total, the cost of stroke to the healthcare system in the USA was $36.5 billion in 2010 [1].

Statistics in other countries are similar to those seen in the USA. The Oxford Vascular Study, which compiled stroke statistics for every person in the county of Oxfordshire in the UK, demonstrated an overall incidence of 1.62 strokes per 1000 per year [4]. The World Health Organization (WHO) Multinational MONItoring of trends and determinants in CArdiovascular disease (MONICA) study looked at 21 populations in 11 countries (10 in Europe plus China) and found an incidence of 125–361 per 100 000 men, and 61–194 per 100 000 women [5].

Diabetes as a risk factor for stroke

There is strong evidence that diabetes mellitus, whether type 1 diabetes or type 2 diabetes, is a significant risk factor for ischaemic cerebrovascular disease (Table 51.1). Observational studies have demonstrated associations between the two diseases. A model created from data from the Framingham Heart Study showed that diabetes confers an increased relative risk (RR) of 1.4 in men and 1.72 in women [6]. The Honolulu Heart Study showed that diabetes increases the risk of thromboembolic stroke two- to threefold over individuals without the disease in Japanese men living in Hawaii [7]. A 2019 meta-analysis found the prevalence of diabetes in ischaemic stroke to be as high as 33% [8].

The effect of diabetes is stronger in ethnic minority populations in the USA. The Greater Cincinnati and Northern Kentucky Stroke Study found that as a sole risk factor, diabetes increased the odds ratio (OR) for having an ischaemic stroke by 2.1 in people of white European ancestry; however, in African Americans, that OR was increased by 2.7. These results held true across all age cohorts [9].

Similarly, the Northern Manhattan Study found that diabetes was a stronger risk factor for ischaemic stroke among African Americans and Caribbean Hispanics than among white Europeans. In these ethnicities, diabetes increased stroke risk by 1.8 and 2.1, respectively, partly due to increased prevalence of the disease. The fraction of strokes that could be directly attributable to diabetes as

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Table 51.1 Risk factors for stroke.

Hypertension
Diabetes
Tobacco use
Hyperlipidaemia
Atrial fibrillation
Carotid artery disease

a risk factor was 14% among African Americans and 10% among Caribbean Hispanics [10].

The Copenhagen City Heart Study found a difference in the effect of diabetes among men and women. Thus, while diabetes increased the RR of first stroke, incident stroke, and hospital admission for stroke among men by 1.5–2, among women the same RRs were increased by 2.0–6.5 [11].

In addition to its effects as a sole risk factor, diabetes also exacerbates the effects of other risk factors. Thus, in people with isolated systolic hypertension, diabetes confers additional risk of ischaemic stroke or transient ischemic attack (TIA).

Stroke in people with diabetes

In epidemiological studies, ischaemic stroke occurs at a younger age in individuals who have diabetes. They are also more likely to be African American. Among other risk factors, people with diabetes who have ischaemic stroke are more likely to have hypertension and hyperlipidaemia, and to have experienced a myocardial infarction in the past [9].

Diabetes is a negative predictor for functional outcome following strokes, and most studies have demonstrated longer hospitalizations after stroke in people with diabetes, increased readmission rates, and increased stroke recurrence [8]. Furthermore, diabetes increases the risk of death from stroke. In a prospective study in a Finnish cohort, men had an increased RR of 6 for mortality from ischaemic stroke, whereas women had an RR of 8.2. These RRs were higher than those for systolic blood pressure, smoking, or total serum cholesterol. In this cohort, the fractions of stroke deaths directly attributable to diabetes were 16% in men and 33% in women [12].

In terms of stroke subtype, diabetes is most commonly associated with lacunar infarcts; that is, a small, deep infarct in the region of a single penetrating arterial branch. Conversely, the highest prevalence of diabetes is found in people with demonstrated microvascular disease. Similarly, lacunar disease is more likely to be associated with diabetes than haemorrhages in the same location [13–16] (Figure 51.1).

Diabetes is also associated with both extracranial and intracranial stenosis. In a study of 510 people referred for asymptomatic carotid bruits, only 200 had extracranial stenosis by Doppler examination. There were 66 with asymptomatic intracranial stenosis, of whom 37 had concurrent extracranial stenosis. Of those with intracranial stenosis, 19 had diabetes [17] (Figure 51.2). Interestingly, a recent analysis of the Secondary Prevention of Small Subcortical Strokes (SPS3) study demonstrated that people

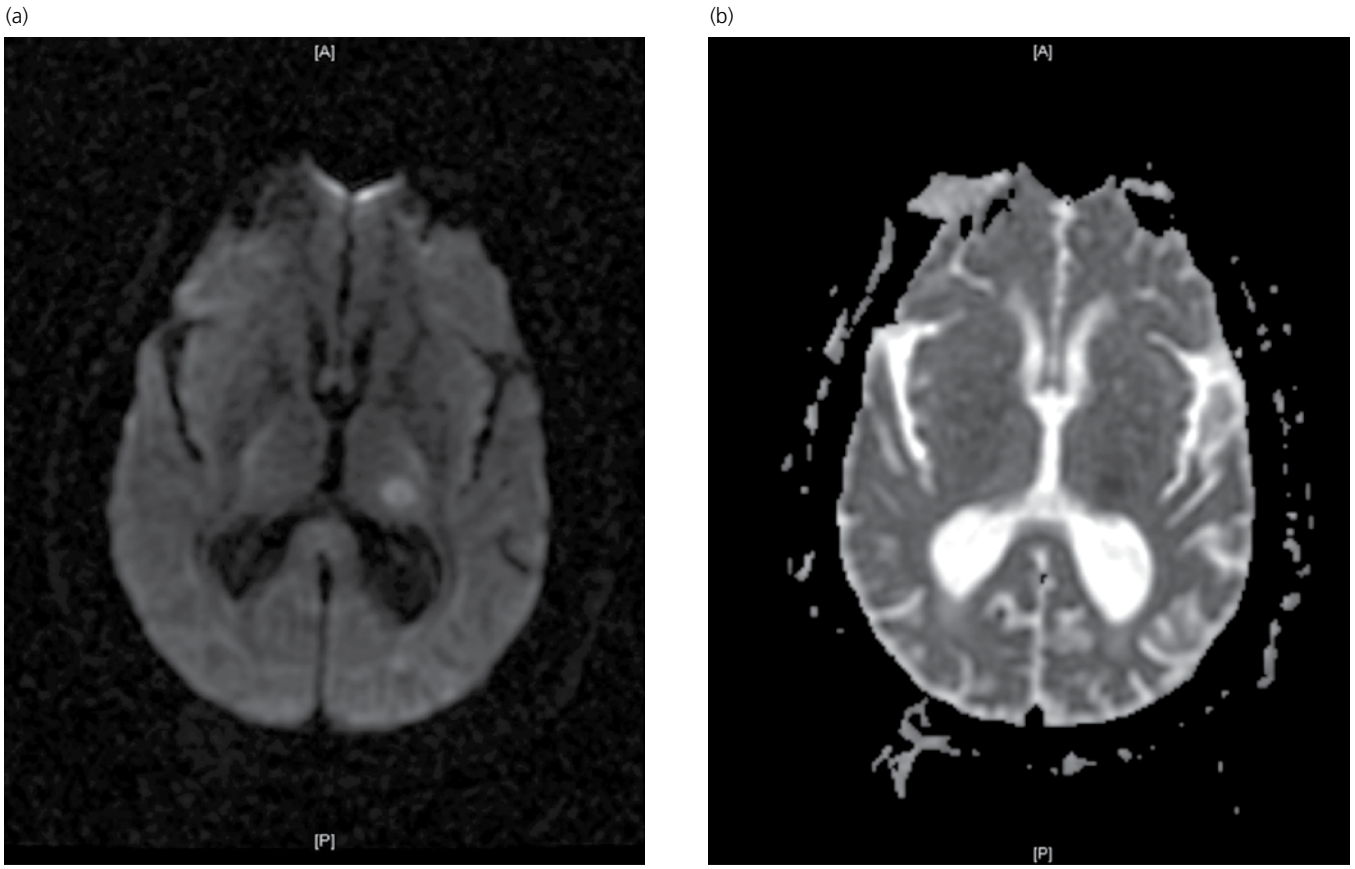

Figure 51.1 Lacunar infarct in the left posterior thalamus. (a) Diffusion-weighted imaging, showing hyperintensity in the area of restricted diffusion, corresponding to acute ischaemia. (b) Apparent diffusion coefficient image corresponding to the slice seen in (a), demonstrating hypointensity in the same distribution, confirming the presence of acute ischaemia.

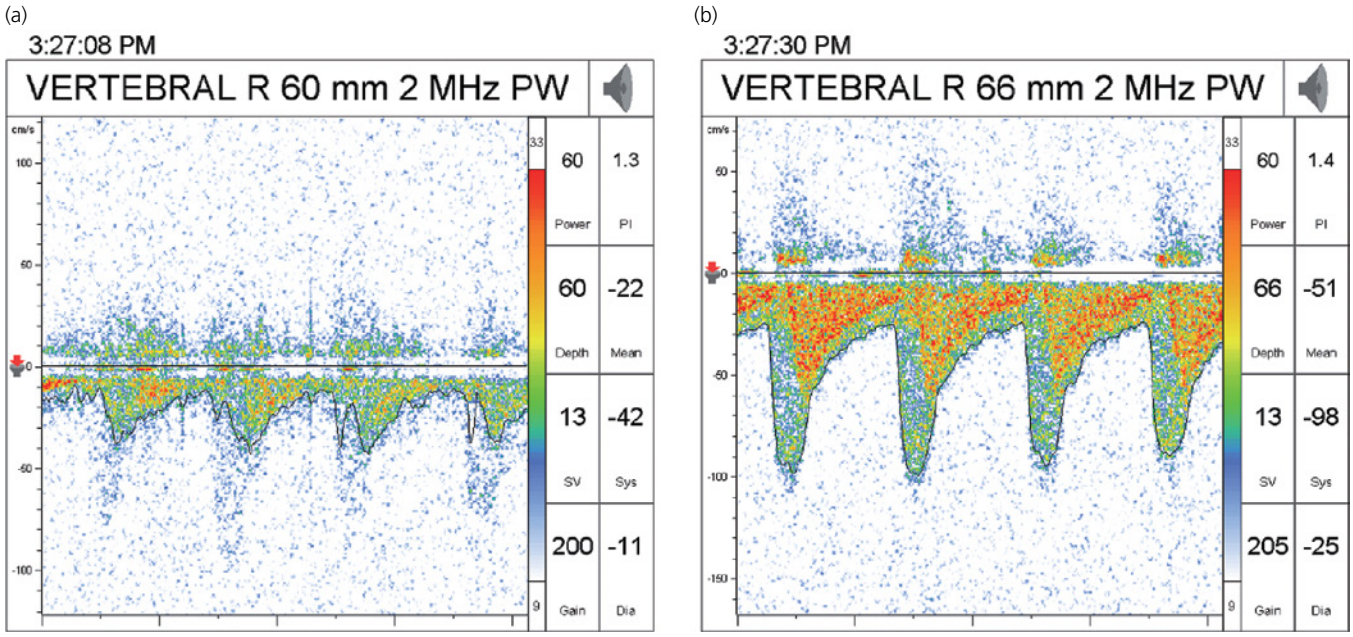

Figure 51.2 Intracranial vertebral artery stenosis as seen by transcranial Doppler ultrasound: (a) normal flow pre-stenosis; (b) increased velocity of flow post-stenosis.

with diabetes and lacunar strokes had higher rates of intracranial stenosis, although whether this causally related to the infarct is not clear [18].

TIA is less common in people with diabetes than in those without. This may indicate that people with diabetes are more likely to present with completed infarct rather than reversible ischaemia [19]. However, individuals with diabetes who do present with TIA are more likely to go on to a full-blown ischaemic stroke in the following two days, as predicted by the ABCD2 score, representing the predictive factors of age >60 yr, blood pressure >140/90 mmHg, clinical features of motor or speech involvement, duration >60 min, and diabetes [20].

Diabetes is a risk factor for coronary artery disease, and therefore for myocardial infarction and subsequent development of atrial fibrillation. In one large retrospective study of the relation between diabetes and atrial fibrillation or atrial flutter, diabetes was found after logistic regression to be a strong independent predictor for atrial arrhythmias in a review of over 850 000 charts over a 10-year period. The OR found for diabetes was 2.13, 95% confidence interval (CI) 2.10 to 2.16 [21]. In turn, atrial fibrillation has been repeatedly demonstrated to be a strong risk factor for cardioembolic stroke, with an estimated 75 000 strokes per year attributable to the arrhythmia [22].

Furthermore, diabetes increases the risk of cardiac embolization. The CHADS2 score is a validated method of stratifying risk of cardioembolic stroke in people with atrial fibrillation. It assigns one point each for the presence of congestive heart failure, hypertension, age >75 yr, and diabetes, and two points for previous stroke or transient ischaemic attack. Each point increase was associated with a 1.5-fold increased risk of stroke. Diabetes alone, then, would increase the risk of stroke in a person with atrial fibrillation from 1.9 to 2.8 [23]. Although the CHADS2 score is not perfect, and attempts have been made to improve its precision [24], it has the benefit of being very easy to use, thus guiding the non-stroke practitioner towards using anticoagulation in the appropriate section of the population.

From large observational studies, there does not appear to be an association between diabetes and haemorrhagic strokes. However, in the Haemorrhagic Stroke Project, a case–control study of young people with intracerebral haemorrhage, diabetes conferred an adjusted OR of 2.4. The risk factor with the most impact was, as predicted, hypertension, which outweighed the contribution from diabetes by more than twofold [25].

Pre-diabetes and other risk factors

Whereas it is well established that diabetes is a strong risk factor for ischaemic stroke, forms of pre-diabetes are not so clearly indicated as risk factors. Selvin et al. studied individuals with and without diabetes in the Atherosclerosis Risk In Communities (ARIC) trial and compared glycated haemoglobin (HbA_{1c}) levels drawn at a specified visit, not necessarily related to the time of the incident stroke [26]. With increasing tertiles of glycation across the normal distribution within each group, the risk of stroke increased in both cohorts, although it was only in those with diabetes that the difference achieved statistical significance.

In contrast, Myint et al. abstracted data from the European Prospective Investigation into Cancer (EPIC) on HbA_{1c} levels in persons without known diabetes and correlated these data with stroke risk [27]. In this population, it was only after levels were higher than 7.0% (53 mmol/mol) that an increased risk of stroke was demonstrated, compared with those with HbA_{1c} <5.0% (31 mmol/mol). Given that these individuals most likely actually had undiagnosed diabetes, this finding may not implicate chronic hyperglycaemia alone as the primary risk factor for stroke.

Insulin resistance, another element of type 2 diabetes, likewise has demonstrated conflicting evidence for association with stroke. The ARIC study investigated hyperinsulinaemia in people without diabetes and found a mild increase in risk of stroke of 1.19 with each increase of 50 pmol/l of fasting insulin. After adjustment for

other risk factors such as age, systolic blood pressure, and smoking, the increase in risk was not as well defined [28].

Obesity, a proxy for insulin resistance and pre-diabetes, has also been linked to stroke through several epidemiological studies. For example, the Copenhagen City Heart Study found that body mass index (BMI) was independently associated with increased risk of stroke [29]. Similarly, the Nurses' Health Study found, as expected, an increasing risk of stroke with increasing BMI, with an RR of stroke of 2.37 (95% CI 1.60 to 3.50) seen in people with BMI >32 kg/m^2 [30]. However, the ARIC study did not demonstrate any relationship between BMI and stroke, or between waist/hip ratio, a better measurement of abdominal obesity, and stroke [28]. In addition, when adjustment for cardiovascular risks is performed, the relative risk of BMI for stroke is once again attenuated.

Although these individual forms of pre-diabetes have not conclusively been shown to predispose people to stroke, the constellation of diseases together called the metabolic syndrome has. The combination of hypertension, hyperlipidaemia, insulin resistance, and abdominal obesity creates an environment that is highly susceptible to vascular damage and ischaemic sequelae.

In a Finnish cohort, the metabolic syndrome in the absence of diabetes or cardiovascular disease was associated with stroke with an RR of ~2, after adjustment for multiple other risk factors [31]. Similarly, a cohort from the ARIC study who likewise were free of diabetes, coronary heart disease, or stroke had an increased RR of 1.5–2 for ischaemic stroke. In addition, on separating out each risk factor, there appeared to be a synergistic effect from the combination over the RRs inherent in each component [32].

Pathophysiology of ischaemic stroke in diabetes

Diabetes predisposes individuals to vascular thrombo-occlusive events in several ways. There is accelerated atherosclerosis in both large and medium-sized vessels. There is a disordered endothelial response, and the blood is hypercoagulable [33].

Carotid intima-media thickness (IMT) is a useful proxy for early atherosclerosis, as it is easily measured by Doppler examination. Furthermore, IMT is associated with primary stroke, with an increased RR per standard deviation (0.163 mm) of 1.57 in individuals who had not had a previous stroke [34]. It also predicts recurrent stroke, with each 0.1 mm increase in IMT associated with an increased risk of 18% [35]. Diabetes is associated with increased IMT. The Insulin Resistance Atherosclerosis Study demonstrated an increase in common carotid IMT in people with long-standing diabetes, but not in those with newly diagnosed diabetes. Nor was there an association with internal carotid artery IMT [36].

Conversely, people with diabetes with stroke have been found to have greater IMT. In a study of 438 Japanese people with type 2 diabetes, common carotid IMT was significantly higher in those who had stroke, even after adjustment for age, BMI, and smoking status [37]. Similarly, in a Czech cohort, IMT was increased in people with stroke and diabetes [38]. A recent study on glycaemic indices revealed significant associations between IMT and time in goal glycaemic range, suggesting that better overall glycaemic management reduces macrovascular disease [39].

Atherosclerosis also affects the ability of endothelium to release nitric oxide (NO), a potent vasodilator. In diabetes, blood vessels have either reduced NO production or altered NO metabolism. In addition to its vasodilating effects, NO protects against platelet aggregation and enables the blood vessel to withstand ischaemic conditions. With decreased NO activity, the vessel will tend more towards vasoconstriction, with predictably poor response to ischaemia.

People who have suffered a stroke have decreased NO in circulating blood, along with increased peroxynitrite ($ONOO^-$), a reactive oxygen species. These results were particularly evident in larger strokes. Since the measurements were performed for acute stroke, these levels are likely to represent the outcome of ischaemia rather than the cause. However, the correlation supports a role for decreased NO in the effects of stroke [40].

The cerebral vasculature has a diminished response to inhibition of NO synthase (NOS). In a small study of men with diabetes treated with a synthetic NOS inhibitor, N^G-monomethyl-L-arginine, the blood flow through the internal carotid artery was significantly lower than in men without diabetes treated likewise [41].

As further indirect evidence of the role of NO in stroke, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) have multiple beneficial effects beyond their most common one, that of lowering plasma cholesterol. Among these effects are increasing the expression of endothelial NOS and also decreasing the activity of Rho-kinase, a proconstrictor enzyme [42]. Statins lower the risk of recurrent stroke in several large studies [43–45]. Whether the beneficial effect of statins in stroke is due to their cholesterol-lowering effect, their ability to stabilize atherosclerotic plaques, their effects on vascular function, or more likely a combination of all of these is difficult to ascertain.

In addition to these predisposing factors, the blood of someone with diabetes is hypercoagulable. Studies have demonstrated increased thrombin generation [46], increased prothrombin fragments, and increased thrombin–antithrombin III complexes [47]. Furthermore, the elevated prothrombotic levels were significantly associated with macroangiopathic complications.

Thrombus formation is further promoted by platelet hyperreactivity in the blood of individuals with diabetes. In people with metabolic syndrome, platelets have increased activity both through closure time as measured by the platelet function analyser (PFA-100), by increased fibrinogen binding after exposure to adenosine diphosphate, implying activation of the glycoprotein (GP)IIa/IIIb receptors, and by expression of activated ligands on the platelet surface [48]. In diabetes, platelets were hyper-reactive as measured by light transmittance aggregometry and expression of surface ligands [49].

Hence, taken together, the person with diabetes has a vascular environment that is highly susceptible to thrombo-occlusive complications. With early atherosclerosis and disordered endothelial response, the person with diabetes is predisposed to thrombophilia. The blood, in its hypercoagulable state combined with platelets that are highly active in themselves, is far more likely to form clots.

Lacunar strokes are caused by damage to smaller parenchymal vessels. The most common cause is microatheroma, as demonstrated in the pathological case series published by Fisher [50–52], the neurologist responsible for naming the lacunar syndromes. Lipohyalinosis and fibrinoid necrosis also cause microangiopathies, and both are most commonly found in the setting of chronic hypertension of severe acute blood pressure elevations, as seen in hypertensive encephalopathy [53, 54].

Primary prevention of stroke in people with diabetes

Primary prevention of stroke is of paramount importance, as the disability from stroke and healthcare costs associated with the acute and chronic care of stroke are so extensive. The approach to prevention in the person with diabetes is of necessity multifactorial.

Medical therapy aimed at achieving normoglycaemia is the foundation. The Diabetes Control and Complications Trial (DCCT) investigated intensive insulin regimens including subcutaneous insulin injections and external insulin pumps in people with type 1 diabetes. The goal for treatment was HbA_{1c} levels of <6.0% (42 mmol/mol). The comparison group had no such goals apart from prevention of hyperglycaemia or hypoglycaemia [55]. The intensive treatment group achieved a reduction of 57% in the combined endpoints of non-fatal myocardial infarction or stroke, cardiac death, or revascularization procedure. The majority of this improvement was associated with the decrease in HbA_{1c} [55].

The UK Prospective Diabetes Study (UKPDS) did not show any reduction in macrovascular complications of type 2 diabetes despite a 0.9% (10 mmol/mol) reduction in HbA_{1c} in an intensive treatment group. Microvascular complications such as retinopathy and neuropathy were significantly reduced [56]. A 10-year follow-up study of the same cohort after attempts to maintain treatment differences had desisted showed that the original treatment cohort had a persistent decrease in microvascular complications and also in myocardial infarctions and deaths from any cause [57]. Hence glycaemic management, at least in type 2 diabetes, has not been linked to a reduction in risk for stroke.

Among oral anti-diabetes agents, metformin was the first to be shown to decrease diabetes-related endpoints including stroke by 32% and diabetes-related mortality including from stroke by 42% compared with conventional therapy in UKPDS. Furthermore, it was more effective in reducing these outcomes compared with other intensive therapies such as sulfonylureas (e.g. chlorpropamide or glibenclamide) or insulin. However, it should be noted that HbA_{1c} was similar among the groups, so the benefits obtained were not explicable on the basis of improved glycaemic levels [58].

Rosiglitazone, a thiazolidinedione, on the other hand, has been linked with increased risk of myocardial infarction and death from cardiovascular causes, although stroke was not assessed separately in the meta-analysis reporting these findings [59]. However, in the RECORD trial, treatment with rosiglitazone was associated with a trend towards a decreased risk of stroke during the follow-up period, although this finding was somewhat offset by an increased risk of heart failure. In addition, the control group was less likely to be treated with statins, which may confound the decreased risk of stroke [60]. Pioglitazone, another medication in the same class, was not associated with worse cardiovascular outcomes including stroke, and in fact reduced a secondary outcome of all-cause mortality, non-fatal myocardial infarction, and non-fatal stroke by 16% [61].

Further trials on the effects of glucagon-like peptide 1 (GLP-1) receptor agonists and sodium–glucose cotransporter 2 (SGLT-2) inhibitors have added little to our understanding of their impact on risk of stroke. For example, the Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) trial found a small but significant reduction in the risk of non-fatal stroke for people treated with the GLP-1 receptor antagonist dulaglutide, but no difference in fatal strokes [62]. The EMPAgliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients–Removing Excess Glucose (EMPA-REG) found a non-significant increased risk in both fatal and non-fatal strokes in participants treated with the SGLT-2 inhibitor empagliflozin [63]. At this time, in the absence of strong consistent evidence, it is recommended to utilize metformin as a first-line agent, and then to choose a GLP-1 receptor agonist as the next agent where the prevention of further vascular events is the priority, or an SGLT-2 inhibitor when prevention of worsening heart failure is the priority [64].

Given how susceptible people with diabetes are to the effects of other vascular risk factors such as hypertension and hyperlipidaemia, the therapeutic regimen must also address these states. In treating hypertension in people with diabetes, the classes of medications with effects on the renin–angiotensin system appear to have the greatest benefit (Chapter 47).

The Heart Outcomes Prevention Evaluation (HOPE) trial examined people either with vascular disease (including coronary artery disease or stroke) or diabetes plus one other cardiovascular risk factor, such as hypertension, tobacco use, or elevated low-density lipoprotein (LDL) cholesterol levels. In this high-risk population, ramipril, an angiotensin-converting enzyme (ACE) inhibitor, decreased the risk of death from cardiovascular causes with an RR of 0.74, and reduced the risk of stroke with an RR of 0.68. As the mean reduction in blood pressure was only 3/2 mmHg, the benefits were not attributable to the blood pressure–lowering effect of the medication. The effect was similar whether or not the participants had had a stroke prior to enrolment [65].

The LCZ696 in Advanced Heart Failure (LIFE) trial examined people with diabetes, hypertension, and left ventricular hypertrophy. Participants were treated with either losartan, an angiotensin-2 receptor antagonist, or atenolol. Although, again, both medications achieved the same reduction in blood pressure, the primary endpoint of cardiovascular mortality, myocardial infarction, or non-fatal stroke was reduced with an RR of 0.76. Notably in this trial only 40% of participants achieved a systolic blood pressure of <140 mmHg, implying that further benefits would likely accrue with more intensive management [66].

A trial of intensive multifactorial medical management in individuals with diabetes with microalbuminuria showed a reduction in all-cause mortality, cardiovascular mortality, and cardiovascular events. The regimen was designed to achieve the following goals: HbA_{1c} <6.5% (48 mmol/mol), fasting total serum cholesterol <175 mg/dl (4.5 mmol/l), systolic blood pressure <130 mmHg, and diastolic blood pressure <80 mmHg. Stroke was not a prespecified endpoint in this study; however, there were 6 strokes in 6 participants in the intensive medical group, compared with 30 strokes in 18 participants in the control group [67].

Antiplatelet treatment for the primary prevention of major adverse cardiovascular events has undergone a reversal in recent years, due to the publication of large trials that have failed to show a good risk-to-benefit ratio [68]. The Antithrombotic Trialists' Collaboration meta-analysis did not demonstrate a significant improvement in the primary prevention of ischaemic stroke in people with diabetes. Overall, nearly 5000 people were treated with aspirin, with only a 7% reduction in serious vascular events. The 95% CI was wide enough to include a possible 25% risk reduction, a value that is consistent with the prevention of secondary stroke in this population [69]. However, A Study of Cardiovascular Events iN Diabetes (ASCEND) found only a non-significant trend towards risk reduction of 12% [70]. Currently, low-dose aspirin of at least 70 mg/d is recommended for primary prevention of cardiovascular events only for those with diabetes at high risk of such events.

Most of the early trials of antithrombotic medications were performed only on men. In the Women's Health Study, a study performed among female health professionals with no history of coronary or cerebrovascular disease, low-dose aspirin (100 mg every other day) was associated with a 17% risk reduction in stroke, a result of a 24% risk reduction in ischaemic stroke, and a non-significant increase in haemorrhagic stroke. These findings were especially pronounced in women older than 65 years of age at the time of enrolment, and also in the subgroup with diabetes [71].

Treatment of acute stroke in persons with diabetes

Treatment of acute stroke is limited by the vulnerability of the neuron to ischaemic insult. With decreasing cerebral blood flow, the parenchyma becomes less likely to recover from even short-duration ischaemia. With cerebral blood flow <20 ml/100 g of tissue, neurological dysfunction begins to appear. However, it is not until the cerebral blood flow falls below 10 ml/100 g of tissue that irreversible ischaemia occurs, in a matter of minutes [72].

Thrombolysis is effective in the treatment of acute stroke provided that the medication is given within the first three hours after symptom onset, as defined by the last time the individual was seen at their neurological functional baseline (Table 51.2). The National Institute of Neurological Disorders and Stroke (NINDS) trial of intravenous tissue plasminogen activator (t-PA) demonstrated a 30–50% increased likelihood of minimal or no disability three months after treatment. The thrombolysis was associated with a 6.4% chance of symptomatic intracranial haemorrhage, but the mortality data at three months were not statistically different between the treatment and the placebo groups [73]. Based on this trial, treatment with intravenous t-PA became standard of care in this early time period. The European Cooperative Acute Stroke Study III (ECASS-III) trial [74] also suggested that it is not only safe but also clinically effective to a lesser extent in a select group to give intravenous t-PA in the window between 3 and 4.5 hours after the onset of symptoms. However, individuals with diabetes who had had a previous stroke by history or on imaging were excluded from the trial.

Thrombolysis in the person with diabetes with acute stroke is not as successful as in the general population. In a series of 27 individuals treated with intravenous t-PA, none of those with diabetes achieved recanalization of the occluded artery as measured by transcranial Doppler ultrasound [75]. The series was not large enough to demonstrate a significant difference. In another study examining which factors might predict major neurological improvement in people treated with intravenous t-PA, there was a trend towards people with diabetes being less likely to achieve that improvement [76]. It has been proposed that the poor collateral circulation seen in those with diabetes accounts for the reduced benefit in t-PA in this population [77].

Beyond intravenous thrombolysis, intra-arterial thrombolysis has been examined up to six hours after the onset of stroke symptoms. The Prolyse in Acute Cerebral Thromboembolism II (PROACT II) trial found that participants treated with intra-arterial urokinase had a 58% RR reduction to achieve minimal or no functional disability at 90 days after treatment. Mortality rates were comparable, and recanalization rates were greatly improved with the medication [78]. Current guidelines support the use of intra-arterial thrombolysis in the period between three and six hours after the onset of symptoms. However, the medication has not been approved by the US Food and Drug Administration (FDA) for this indication [79].

In a case series of 100 people treated with intra-arterial thrombolysis with urokinase, diabetes was associated with poor functional outcome at three months. It was not associated with symptomatic intracranial haemorrhage [80]. However, since diabetes is independently associated with worse outcomes following acute ischaemic stroke, it is unclear whether these data have any meaning for clinical practice.

Other interventional techniques include clot retrieval. Three devices have been tested: the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) device (UCLA, Los Angeles, CA, USA), a corkscrew-type device; the Penumbra System® (Penumbra, Alameda, CA, USA), a direct clot aspirator; and the Solitaire™ stent retrieval system (Coviden, Mansfield, MA, USA). The last device is the one most commonly used clinically today: compared with the MERCI device, it had improved chances of restoring partial or complete restoration of blood flow with an OR of 4.87 [81]. In support of the use of interventional therapy, the Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN) trial enrolled 500 people and randomized them to endovascular intervention plus usual care (which could include intravenous t-PA) versus usual care alone. The majority of interventional treatments used stent retrieval. The interventional group had an absolute risk reduction of achieving a good functional outcome of 13.5%, with a number needed to treat of 7.4 [82]. The more recent Highly Effective Reperfusion using Multiple Endovascular Devices (HERMES) meta-analysis reviews several similar studies across multiple populations worldwide. The results align with those of MR CLEAN and provide overwhelming evidence for the use of mechanical thrombectomy in the setting of acute ischaemic stroke [83].

Follow-up studies have sought to extend the window in which people may undergo mechanical thrombectomy. The DWI or CTP Assessment with clinical mismatch in the triage of Wake-up and late presenting strokes undergoing Neurointervention with Trevo (DAWN) and Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE-3) trials utilized computed tomography (CT) and magnetic resonance (MR) perfusion technology to extend the thrombectomy window up to 24 hours from symptom onset. Both studies demonstrated significantly improved outcomes at 90 days without increase in adverse events like intraparenchymal haemorrhage [84, 85]. These landmark studies all follow the

Table 51.2 Management of acute ischaemic stroke.

0–3 h Intravenous tissue-plasminogen activator (t-PA)
0–6 h Intra-arterial t-PA
0–24 h Mechanical clot retrieval (stent retriever device) in appropriately selected individuals
Permissive hypertension for the first 3–5 d
Aspiration precautions
Deep vein thrombosis (DVT) prophylaxis

Intravenous t-PA is the only acute intervention approved by the US Food and Drug Administration. Both intra-arterial t-PA and mechanical clot retrieval remain experimental, although widely used. Intravenous t-PA should remain the standard of care when it is not contraindicated, with the other interventions to be used as auxiliary therapy.

Interventional Management of Stroke (IMS-III) trial, which demonstrated no increased risk nor benefit to endovascular therapy after treatment with intravenous t-PA [86], though analysis of this study shows that many participants did not have an appropriate target thrombus [87].

Hyperglycaemia at the time of stroke treatment is associated with worsened outcomes. In a series of 73 people treated with intravenous t-PA, age, diabetes, admission glucose >140 mg/dl (7.8 mmol/l), and early reocclusion on transcranial Doppler ultrasound were significantly associated with worsened functional outcome as defined by a score of >3 on the modified Rankin scale. However, after logistic regression, only the hyperglycaemia remained as an independent predictor of poor outcome. In particular, it was associated with larger infarct size, lower degree of neurological improvement, and worse clinical outcome if recanalization was achieved [88].

Similarly, baseline hyperglycaemia is associated with a greater likelihood of going on to symptomatic intracranial haemorrhage after intravenous thrombolysis. There appears to be a dose–response relationship between plasma glucose levels and likelihood of haemorrhage. This was especially true when levels were above 11.1 mmol/l (200 mg/dl), where 25% suffered symptomatic intracranial haemorrhage. In a repeat analysis substituting the presence of diabetes for glucose levels, diabetes was associated with an OR of 3.61 for all haemorrhages, and 7.46 for symptomatic haemorrhage [89].

Furthermore, both those individuals who acutely worsened and those who showed lack of improvement at 24 hours were more likely to have elevated blood glucose at baseline. Hyperacute worsening in people treated with either intravenous or intraarterial thrombolysis, or both, was unsurprisingly associated with intracerebral haemorrhage and lack of recanalization. However, it was also associated with higher serum glucose. With every increase of 50 mg/dl (2.8 mmol/l) of glucose, the OR for worsened outcome was 1.50 and the OR for mortality was 1.38. Even in those individuals who achieved recanalization, higher blood glucose predicted worse outcomes [90]. Similarly, serum glucose >144 mg/dl (8.0 mmol/l) and also cortical involvement and time to treatment were independent predictors of lack of improvement at 24 hours after treatment with intravenous thrombolysis. The OR for hyperglycaemia was 2.89. Furthermore, lack of improvement at 24 hours predicted poor functional outcome at three months [91].

Although these data are understandably disheartening, they should by no means be taken to imply that people with diabetes and acute stroke should not receive thrombolysis, or that these individuals do not benefit from the treatment. Furthermore, it is not clear whether the hyperglycaemia seen in people with acute stroke and diabetes is secondary to the ischaemic insult as a stress response, or instead part of the chronic diabetic state and thus purely a complicating factor.

Interestingly, one study examined how persistent hyperglycaemia differed from transient hyperglycaemia in functional outcomes in addition to mortality. When hyperglycaemia was present at baseline and when measured 24 hours after admission, it was inversely associated with neurological improvement in the first 7 days, 30-day functional outcome, and 90-day negligible dependence. At the same time, persistent hyperglycaemia was positively associated with increased mortality at 90 days and parenchymal haemorrhage. When hyperglycaemia was absent at baseline but present at 24 hours after admission, it was likewise inversely associated with 90-day negligible dependence and positively associated with death and parenchymal haemorrhage. In this study, baseline hyperglycaemia alone (without persistence at 24 hours) was not associated with poor outcomes. These data suggest that it may not be the stress response hyperglycaemia that causes damage in the acute stroke setting [92].

However, intensive treatment of hyperglycaemia may be associated with improved outcomes, as has been demonstrated for myocardial infarction [93]. A small pilot study found that hyperglycaemia could be treated with insulin infusions safely, but the numbers were too small to compare functional outcomes at one month [94]. In another study to maintain glucose levels between 5.0 and 7.2 mmol/l (90–130 mg/dl) in people with acute ischaemic stroke, the use of insulin drips started no later than 12 hours after the onset of symptoms was associated with a trend towards better functional outcomes and minimal or no neurological symptoms, as measured by the National Institutes of Health (NIH) stroke scale. There were hypoglycaemic episodes in the group treated with continuous infusion, but the majority of these were asymptomatic [95]. Clearly, further study is required on this subject.

Hyperglycaemia as defined by serum glucose >400 mg/dl (22.2 mmol/l) was a contraindication for inclusion in the NINDS trial for some of the reasons discussed, and also because extreme hyperglycaemia can cause focal neurological deficits that mimic stroke [73]. Current guidelines recommend starting aggressive glycaemic management if serum glucose is >200 mg/dl (11.1 mmol/l), while acknowledging that levels above 140–185 mg/dl (7.8–10.3 mmol/l) may still be harmful [79]. Although it may be reasonable to attempt to bring down the glucose level and see if any focal symptoms improve or resolve, and then treat with thrombolysis if no improvement is seen, this approach has yet to be tested.

In terms of oral anti-diabetes agents in the acute stroke setting, one study looked at the role of sulfonylureas taken pre-stroke and during the acute hospitalization. Sulfonylureas have an effect on $NC_{Ca\text{-}ATP}$ channels, which are regulated by the SUR1 receptor, like pancreatic β cells, and are open only during ischaemic episodes, causing cell death. Theoretically, then, treatment with sulfonylureas should be neuroprotective during ischaemia. Although the numbers were small, and people with more severe strokes (NIH stroke scale >9) were excluded, those on the medication were more likely to have a decrease of 4 points on the NIH stroke scale or a score of 0, and were more likely to achieve an excellent functional recovery at discharge. The effect was particularly noticeable in non-lacunar strokes [96].

Further care for the person with acute stroke is best handled in a certified stroke unit, with multidisciplinary care from a team consisting of vascular neurologists, stroke-trained registered nurses, physical therapists, occupational therapists, and speech and swallow specialists. This care results in a reduction in mortality of ~25% [97].

Blood pressure control in acute ischaemic stroke is a subject of ongoing debate. Current thinking still supports the concept of permissive hypertension in the peri-stroke period. Most vascular neurologists would allow the blood pressure to remain untreated until the systolic blood pressure rises above 220 mmHg or the diastolic blood pressure above 120 mmHg. The period when permissive hypertension should be allowed is also controversial. Typically, the blood pressure is left untreated for the first 3–5 days after stroke [79].

The majority of medical complications after stroke relate to the disability associated with neurological deficits. However, deep venous thrombosis and aspiration pneumonitis are two preventable complications. Prevention of deep venous thrombosis is accomplished through subcutaneous anticoagulation with either heparin or low molecular weight heparin with or without external

compressive devices [79]. Initiation of treatment is typically immediately on admission, regardless of the size of infarct. One unblinded study studied heparin versus enoxaparin and found a reduction in thrombosis with the low molecular weight heparin [98].

Prevention of aspiration is more complicated. Protection of the airway is often compromised in the acute period after stroke. Frequent suctioning and positioning help to prevent aspiration. Swallow evaluations should be undertaken before oral nutrition is started in anyone in whom dysphagia is suspected. Placement of nasogastric tubes (NGTs) is often required for nutrition, and frequently patients will require a percutaneous endoscopic gastrostomy (PEG) tube for long-term provision of nutrition. Hydration is necessary, either intravenously before enteral access is established, or via NGT or PEG tubes to prevent dehydration and electrolyte abnormalities. Antibiotics should be started where infection is suspected, and fever should prompt an aggressive search for a source. Hyperthermia itself causes neurological deterioration, so antipyretics should be administered [79].

Secondary prevention of stroke in diabetes

The management of the people with diabetes after stroke is similar to that for primary prevention as already outlined. The eighth report of the Joint National Committee on Prevention and Treatment of Hypertension recommends that people with diabetes should be treated to a blood pressure target of <140/90 mmHg, and that it may take multiple antihypertensive medications to achieve this goal [99]. As suggested by the studies described earlier, ACE inhibitors and angiotensin receptor blockers provide greater protection against cardiovascular events including stroke.

Similarly, the American Heart Association and the American College of Cardiology have published guidelines on the management of cholesterol in individuals with diabetes [100]. All people who have clinical atherosclerotic cardiovascular disease, including stroke or TIA, should be offered treatment with a statin medication, at high intensity if there are no known safety concerns. In the situation where such an event has not occurred, people with diabetes and an LDL cholesterol >70 mg/dl (1.8 mmol/l) should also be treated with a statin. The guidelines suggest a goal of lowering the LDL cholesterol by 50% when high-intensity statin treatment is used. Guidelines from the Endocrine Society likewise endorse aggressive lowering of LDL cholesterol without specific goal thresholds for treatment [101].

Antiplatelet therapy should be started in all people who have had a non-cardioembolic ischaemic stroke (Table 51.3). Although the Antithrombotic Trialists' Collaboration meta-analysis did not show benefit in people with diabetes, *post hoc* analysis of data from the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study found that such individuals treated with clopidogrel had a decreased rate of stroke, myocardial infarction, or death of 15.6% compared with a 17.7% risk in those treated with aspirin [102]. Similarly, in a *post hoc* subgroup analysis of a study of cilostazol, people with diabetes had a decreased rate of recurrent stroke on the medication compared with placebo, with a relative risk reduction of 41.7%. This finding was especially evident in those with lacunar stroke [103]. These findings need to be verified with further trials. The use of a combination of dipyridamole and aspirin was not demonstrated to be non-inferior to clopidogrel in the prevention of recurrent stroke in the Prevention Regimen For Effectively avoiding Second Strokes (PRoFESS) trial. The prevalence of diabetes in this study was 28% in each group, and subgroup analysis within diabetes likewise did not demonstrate any difference between the two treatments [104].

In individuals who have had ischaemic stroke secondary to extracranial carotid stenosis, carotid endarterectomy remains the preferred treatment of choice for carotid artery stenosis >70% (Figure 51.3). For degrees of stenosis between 50% and 70%, the benefits of surgery are much smaller, and decisions to treat will depend on the complication rate at local institutions [31]. However, the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) suggests that carotid artery stenting is equivalent to surgical revascularization with respect to rates of periprocedural stroke, myocardial infarction, or death, or rate of recurrent stroke. However, periprocedural stroke was more likely in the stenting group, whereas myocardial infarction was more likely in the endarterectomy group. People younger than 70 years fared better when stented, whereas those over 70 years had better outcomes when they received endarterectomy. This dichotomization likely represents

Table 51.3 Prevention of ischaemic stroke in the person with diabetes.

Tight glycaemic management
Antihypertensives with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers
Anti-cholesterol treatment, especially with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins)
Health behaviours modifications (tobacco cessation, weight loss, etc.)
Antiplatelet therapy (either aspirin, clopidogrel, or dipyridamole)
Anticoagulation in people with atrial fibrillation

Figure 51.3 Computed tomography angiography with iodinated contrast of the neck. There is mild stenosis seen at the origin of the right internal carotid artery. There is critical stenosis (*string sign*) at the origin of the left internal carotid artery, corresponding to severe atherosclerotic plaque.

the risk of undergoing an endovascular procedure with an increasing atherosclerotic burden [105].

People with diabetes with atrial fibrillation, paroxysmal or otherwise, should be anticoagulated with warfarin to a goal of an International Normalized Ratio (INR) of 2.0–3.0. The risk reduction associated with treatment with anticoagulation is 68%, with an absolute risk reduction in the annual stroke rate from 4.5% to 1.4% [106]. This reduction in risk is so strong that one study estimated that a person would have to fall 295 times in one year for the risk of subdural haematoma secondary to trauma to outweigh the benefits gained from anticoagulation [107]. There is no reason to assume that this is any different for people with diabetes.

Several novel oral anticoagulants have been developed for the prevention of stroke in people with atrial fibrillation. Dabigatran [108], a direct thrombin inhibitor, and rivaroxaban [109] and apixaban [110], both direct factor Xa inhibitors, are at least equivalent to warfarin in reducing the risk of recurrent ischaemic stroke, with fewer haemorrhagic complications. These medications have a significant advantage over warfarin, in that they do not require monitoring of levels, nor do they interact significantly with other medications or require dietary adjustment. There is a reversal agent available (andexanet alfa) for treatment of those with bleeding complications while on direct factor Xa inhibitors, with demonstrated effectiveness in normalizing factor Xa levels [111]. Our current first-choice agent for the prevention of ischemic stroke in the setting of atrial fibrillation is apixaban.

Conclusions

Diabetes is a strong risk factor for ischaemic stroke, and stroke in diabetes is both more severe in presentation and outcome and more recalcitrant to acute treatment. Although many aetiologies of stroke are made more common by diabetes, the most common type of stroke found in people with diabetes is lacunar microvascular infarction. Prevention of stroke in the person with diabetes is best served through aggressive management of concurrent hypertension and hyperlipidaemia. Careful glycaemic management also likely reduces the risk of stroke, but the risk reduction is not nearly as robust. Antiplatelet therapy also plays an important role: a single antithrombotic agent is sufficient for the prevention of ischaemic stroke. Hyperglycaemia in the acute phase after ischaemic stroke is associated with poor outcomes, and aggressive management likely improves functional recovery.

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52 Peripheral Vascular Disease

Henrik H. Sillesen
Department of Vascular Surgery, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Key points

- Peripheral arterial disease is very common, affecting up to 30% of all people with diabetes.
- Amputations are much more common in people with diabetes and occur 5–8 times more often than in those without diabetes.
- Atherosclerosis is common in people with diabetes, and measurement of ankle blood pressure may identify individuals with symptomatic peripheral arterial disease, but also people at an early asymptomatic stage.
- People with diabetes have atherosclerotic lesions located more peripherally than those without diabetes and therefore are more commonly inoperable for technical reasons.
- People with diabetes have more complications in surgery, both locally (infections) and systemically (e.g. cardiac, pulmonary), than those without diabetes.
- Treatment of atherosclerosis in people with diabetes is basically the same as in those without diabetes.

Peripheral vascular disease includes diseases to arteries and veins outside the thoracic region. Because of space limitations, this chapter mainly covers the three most common arterial diseases:

- Peripheral arterial disease (insufficient blood supply to the lower limb).
- Carotid artery disease.
- Aortic aneurysms.

Other, rarer manifestations of atherosclerotic disease (e.g. renovascular hypertension, abdominal angina, and ischaemia of the upper extremities) are mentioned briefly. Special considerations in individuals with diabetes are dealt with in relevant sections, for example infection in an ischaemic foot in a person with diabetes is described in the section that includes critical limb ischaemia.

Atherosclerosis is the main cause of peripheral arterial disease, and the overall pathogenesis is covered in Chapter 46. It is important to appreciate that the pathogenetic mechanisms of clinical atherosclerosis are dual: chronic obstructive and thrombotic. Although the chronic obstructive mechanism is the main cause of lower-limb ischaemia, including in people with diabetes, it is often preceded by a thrombotic event: a person with mild *claudication* (pain when using the leg) suddenly experiences a significant shortening of walking distance or sudden onset of rest pain. Alternatively, the seemingly healthy person suddenly develops claudication. A myocardial infarction or stroke in a person with chronic obstructive arterial disease and claudication is also a thrombotic event.

In general, individuals with diabetes more often develop symptoms of atherosclerotic complications, they do so at a younger age, they are more difficult to treat, and they have more complications with treatment (especially with invasive treatment).

Peripheral arterial disease

Peripheral arterial disease is a chronic condition that, like atherosclerosis in other vascular beds, develops over decades. The World Health Organization (WHO) definition includes exercise-related pain and/or ankle brachial index (ABI) <0.9. On average, symptoms from the lower limbs develop 5–10 years later than from the coronary circulation. Acute ischaemia may develop because of:

- Thrombosis in a vessel with pre-existing atherosclerotic plaques and/or stenosis.
- Embolism (e.g. from mural thrombus in the heart or from an arterial lesion upstream).
- Trauma.

Peripheral arterial disease is traditionally divided into four stages (Fontaine):

1. Asymptomatic (ABI <0.9).
2. Functional pain (claudication).
3. Rest pain.
4. Non-healing ulcers or gangrene.

Diabetes is a major contributor to peripheral arterial disease.

Incidence

In population-based studies in Western Europe, the incidence of symptomatic peripheral arterial disease is 3–4% among 60–65-year-old individuals, increasing to 15–20% in people aged 85–90 years [1–3]. Similar findings have been reported in the USA. The incidence of asymptomatic cases where the ABI is <0.9 is much higher, ~20% of

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all people above 65 years of age, ranging from 10% in those aged 60–65 years to almost 50% in those aged 85–90 years [1–3]. Critical limb ischaemia, defined as ABI <0.4 or rest pain and/or non-healing ulcers, occurs in 1% of people aged 65 years or older.

Prevalence of peripheral arterial disease in people with diabetes

The prevalence of peripheral arterial disease in people with diabetes depends on the usual atherosclerosis risk factors and duration of diabetes. There have been only a few demographic studies of the general population. Using ABI <0.9 as the selection criterion, Lange et al. [4] found a prevalence of 26.3% in people with diabetes compared with 15.3% in people without diabetes on screening 6880 Germans above 65 years of age, of whom 1743 (25%) had diabetes. Similar findings have been reported by others: 20–30% of those with diabetes have peripheral arterial disease [5, 6]. Claudication is twice as common in people with diabetes as those without diabetes.

Pathophysiology

The pathophysiology of peripheral arterial disease is described in detail in Chapter 46; however, in brief, the pathophysiology in people with diabetes is similar to that in people without diabetes. The abnormal metabolic state that accompanies diabetes directly contributes to the development of atherosclerosis. Proatherogenic changes include increases in vascular inflammation and alterations in multiple cell types. Both mechanisms of atherosclerotic complications are of importance in peripheral arterial disease (gradual narrowing resulting in stenosis and acute thrombosis in existing atherosclerotic lesions). The long-term accumulation of lipids in the vessel wall is important and sudden local thrombosis can occur at any time, although in most cases this happens after symptoms (claudication) have developed.

To reach the stage of critical limb-threatening ischaemia, advanced atherosclerosis has developed. Often, multiple segments of the arterial tree from the aorta to the foot are affected (stenotic and/or occluded). In people with diabetes, the atherosclerotic lesions are more peripherally located than in those without diabetes. Whereas the iliac and femoral arteries are most commonly stenotic and/or occluded in individuals without diabetes, in those with diabetes it is most often the crural or pedal arteries that are severely affected by atherosclerosis. In some cases of ischaemic ulcers of the toe in a person with diabetes, foot pulses may be present due to very distal occlusive disease. This poses a challenge for revascularization, because the results are generally better with more proximal reconstruction and worse with distal disease and poor *run-off* (vessels to receive the blood supply as a result of the revascularization procedure).

Perfusion has to be very poor to develop ischaemic non-healing ulcers. The most reliable method for assessment of peripheral perfusion in those with diabetes is measurement of toe pressure. A toe pressure below 20–25 mmHg signals a poor chance of healing of a peripherally located ulcer. The special considerations related to the potentially dramatic course of infection in a diabetic foot are covered in Chapter 53.

Asymptomatic stage

The asymptomatic stage of peripheral arterial disease is especially interesting because it is associated with an approximately threefold increased mortality compared with matched controls [7, 8]. This excess mortality is caused by accompanying cardiovascular disease. Asymptomatic peripheral arterial disease can be identified by a very simple test, measurement of ankle blood pressure. This test takes only a few minutes and is expressed as the ABI, where the ankle pressure is divided by the highest of the two arm blood pressures. In this manner, variations in blood pressure between measurements do not influence the test result. Not only is an ABI <0.9 associated with increased mortality from cardiovascular causes, but also the level of ABI reduction is predictive: the lower the ABI, the worse the prognosis [7]. Identifying an asymptomatic person with an ABI <0.9 is not a case for evaluation with respect to revascularization of the lower limbs, but a case for serious preventive cardiovascular medicine.

Claudication

Claudication is experienced by the individual as pain in lower-limb muscles appearing after walking, most often in the calf, the thigh, and more rarely the buttocks. The walking distance eliciting the pain is very variable, beginning after 10–15 m in severe cases, whereas others may report pain only when walking fast uphill for >500 m. It is important for both clinician and individual with claudication to understand that, although it may be incapacitating for a few and troublesome for many, claudication signals severe vascular disease systemically, and that cardiovascular morbidity and mortality are high (elevated three- to fourfold compared with matched controls).

Rest pain

Rest pain typically begins at night when the individual is in the horizontal position. The positive effect of gravity on lower-limb perfusion is then abolished. The person typically complains about pain in the toes or feet during the night, and most have experienced that standing or sitting up relieves the pain. Many people will sleep sitting in a chair.

In individuals with diabetes, symptomatology may differ because of coincidental peripheral neuropathy. Just as myocardial ischaemia can be masked, symptoms from the lower extremity may be lacking even though peripheral ischaemia exists. This is especially important when a person with diabetes presents with a small ulcer or wound on the lower limb, even if they think that there is a good explanation for developing the ulcer, such as a relevant trauma. The lack of symptoms to signal peripheral ischaemia, combined with the risk of escalating infection in a diabetic foot, has prompted many diabetes healthcare professionals to recommend routine assessment of peripheral circulation at regular intervals in all people with diabetes.

Non-healing ulcers

Non-healing ulcers often begin after minor trauma (e.g. hitting a toe against a chair or wearing shoes that are too small). In some cases, the ulcers develop without any trauma and these will often progress to gangrene if not treated. Ischaemic ulcers develop on the toes or foot, typically at points where shoes are in firm contact. Hence they are usually easy to discriminate from venous ulcers, which are located at the level of the ankles or lower calf.

Rest pain, non-healing ulcers, and/or gangrene are often referred to as critical ischaemia (Chapter 53).

Diagnosis

Most often the history and objective findings will ensure the diagnosis, but measurement of ankle blood pressure will quantify the ischaemia and can be used to monitor changes in the disease (Figure 52.1). In some people with diabetes, the media of smaller arteries become calcified, making them incompressible. Thus, very

Figure 52.1 Measurement of ankle pressure using the Doppler technique.

Figure 52.2 Measurement of toe pressure using the strain gauge technique.

high ankle pressures resulting in elevated ABI (>1.3) signal media sclerosis and should be recognised as a falsely elevated measurement. In fact, ABI >1.3 is associated with a marked increased mortality because media sclerosis is found in people with diabetes and those with renal failure.

Because small arteries are rarely affected by media sclerosis, measurement of toe pressure is an alternative for the assessment of peripheral arterial disease. The strain gauge technique is most commonly used (Figure 52.2), although alternative methods for measurement of toe pressure have been developed recently. Toe pressure is also useful for the prediction of healing of ulcers and amputation wounds.

Prognosis

The risk of amputation is only 1–2% at five years. Around 25% of people with claudication will experience a worsening of their symptoms from the lower legs; however, 75% will be unchanged or improve without revascularization [9]. In contrast, the *systemic* risk is huge; mortality at five years will be 15–25% and even more people will have non-fatal myocardial infarction or stroke.

The risk for a person with diabetes and peripheral arterial disease is much higher than that of a person with peripheral arterial disease only. An individual with diabetes has an eight times greater risk of amputation at the level of the transmetatarsal bones or above than someone without diabetes [10]. In addition to the already severely increased mortality of peripheral arterial disease, people who additionally have diabetes have a further doubling of risk of death [10–12].

Treatment

Treatment of people with symptoms from the lower limb therefore involves two aspects:

- Treatment of symptoms from the lower limb.
- Prevention of cardiovascular complications.

The former includes health behaviour modification, medical therapy, and interventional therapy by either percutaneous transluminal angioplasty (PTA) or open surgery, whereas the latter includes lifestyle modification and preventive medical therapy.

It is beyond the scope of this chapter to detail all aspects of behaviour modification and preventive medical therapy; however, it is extremely important for the reader to understand that individuals with peripheral arterial disease derive at least as much benefit from health behaviour modification and aggressive preventive medical therapy than any other group of people. Most lifestyle changes will benefit the peripheral arterial disease, especially smoking cessation, regular exercise, weight loss, and dietary changes.

Medical prevention follows the same guidelines as for other clinical atherosclerotic manifestations such as ischaemic heart disease and can be summarized as follows: aggressive statin treatment almost irrespective of cholesterol levels, antiplatelet therapy, and blood pressure control. Recently dual-pathway inhibition by low-dose rivaroxaban and aspirin has been shown to reduce major adverse cardiovascular and limb events both in stable peripheral arterial disease and after revascularization [13].

This chapter only discusses details of health behaviour modification and medical therapy relevant to treatment of peripheral arterial disease symptoms, including revascularization by PTA and surgery.

Treatment of symptoms from the lower limb

Most people should be managed without invasive intervention with PTA and/or surgery. Because the risk of cardiovascular complications (cardiac and cerebral) is much higher than the risk of amputation, the main focus should be on preventive measures to halt the atherosclerotic process. The conservative approach with respect to revascularization is especially important for people with diabetes because of the increased risk of surgical complications and poorer results of revascularization. An important exception is critical limb ischaemia, when early revascularization before widespread infection can be limb saving.

Exercise therapy is effective for improving walking distance, and regular exercise for three months can be expected to increase walking distance by 200–250% [14]. Because exercise also reduces cardiovascular morbidity and mortality, it cannot be stressed enough that this is extremely important. Because the effect on walking distance is so good, and because it is important for survival, exercise therapy should always be tried before considering interventional treatment. There are only a few exceptions where interventional treatment may be considered early on:

- Individuals with a very short walking distance, who are not able to carry out important daily responsibilities such as their work.
- Those at risk of amputation (rest pain and non-healing ulcers).

It is challenging to explain to individuals that the symptoms they are experiencing from the lower limb are signalling high cardiovascular risk rather than lower-limb risk. First, there is (or has been) a general perception that atherosclerosis in the limb is less dangerous than in other locations. The author hopes that the introductory remarks in this chapter have changed this potential misperception. Medical therapy for claudication includes as a minimum a platelet inhibitor and statins. In addition to preventing cardiovascular complications, statins have been shown in placebo-controlled trials to improve walking distance by 30–50%.

Interventional treatment

Interventional treatment (endovascular or open surgery) for peripheral arterial disease is indicated when:

- Exercise and other lifestyle modifications have failed to improve symptoms to an acceptable state.
- Claudication is incapacitating.
- Critical limb ischaemia is present (rest pain, non-healing ulcers, and/or gangrene).

Again, for the person with diabetes, the indication for revascularization should be considered very carefully in those with only claudication. The choice between PTA and open surgical management depends on the location and extent of disease. In general, endovascular treatment can be expected to perform well in cases of shorter lesions, whereas open surgery is preferred for extensive occlusive disease. Obviously, whenever comparable results can be obtained, PTA is preferred because it is less invasive and associated with fewer complications than open arterial reconstructions. In people with severe comorbidity that might complicate the outcome of open surgery, PTA would be preferred, even though theoretically surgery would be the treatment of choice if only patency of the revascularization procedure was considered.

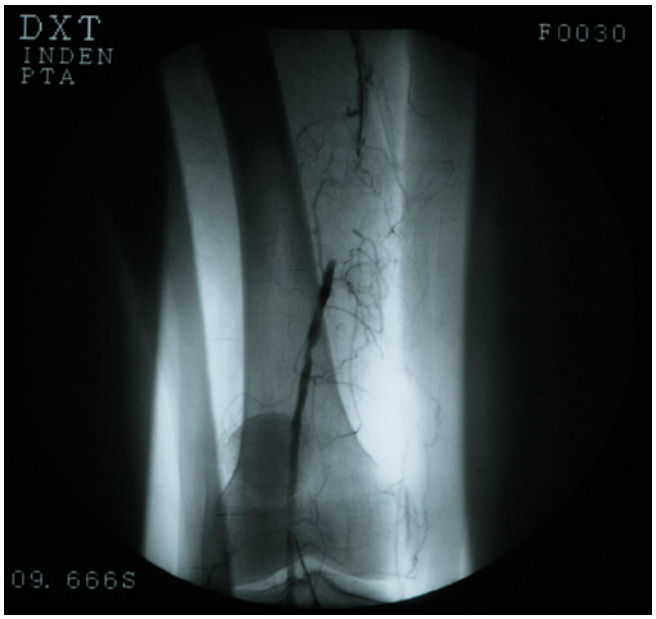
The arterial lesions that cause obstruction of blood supply to the lower limb are most often located in the distal abdominal aorta just proximal to the aorta–iliac bifurcation, in the iliac arteries, and in the common and superficial femoral arteries. The arteries in the calf, the anterior and posterior tibial and the peroneal arteries, are often involved in people with diabetes with critical ischaemia. In general, when individuals with diabetes present with symptoms, they have a more distal involvement with open arteries down to the level of the popliteal artery, and then occlusive disease of the calf vessels and sometimes also the arteries in the foot. The results of revascularization for people with diabetes with toe or foot ulcers are worse than those for the general population, partly because reconstructions yield better results with respect to patency when the lesions are more centrally located.

Percutaneous transluminal angioplasty

In principle, PTA can be performed anywhere between the heart and the feet. In general, the more centrally located the lesions being treated are, the better the results (especially with PTA). Also, the shorter the stenosis or occlusion, the better the results, and stenting improves patency in most cases. Endovascular-treated common iliac arteries, as an example, remain patent in 60–80% of cases after five years, and thereafter they may be redilatated. Primary stenting has become the preferred treatment in most cases. Because serious complications are rare, the tendency to offer PTA for iliac artery obstruction is greater than for occlusive disease that is more peripherally located.

PTA of the superficial femoral artery (Figure 52.3) may relieve symptoms, but the results depend on the extent of disease. With

(a)



(b)

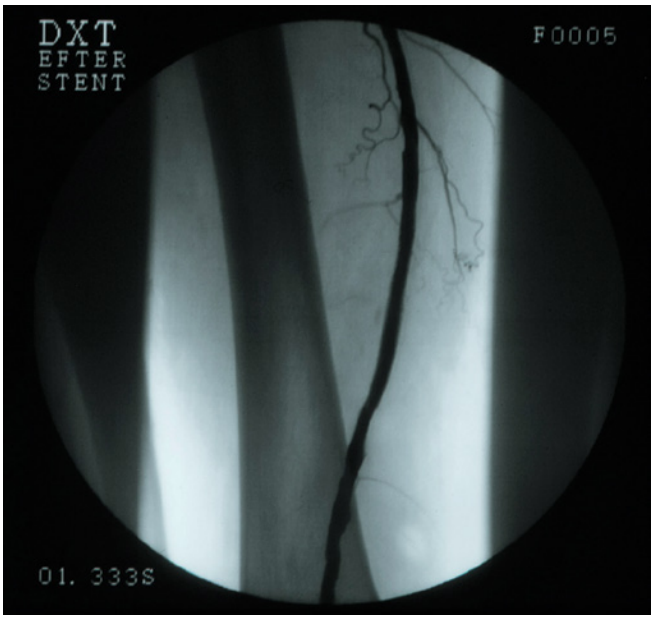


Figure 52.3 Short occlusion of the superficial femoral artery treated with (a) percutaneous transluminal angioplasty and (b) stenting.

Table 52.1 Pooled patency of vascular reconstructions.

Reconstruction	Patency (%)			
	1 yr	3 yr	5 yr	10 yr
Endovascular				
Iliac artery	86	82	71	
Fem-pop stenosis PTA	77	61	55	
Fem-pop occlusion PTA	65	48	42	
Fem-pop stenosis PTA + stent	75	66		
Fem-pop occlusion PTA + stent	73	64		
Open surgery				
Aorto-bifemoral bypass			90	80
Fem-fem crossover			75	
Fem-pop vein			80[a]	
Fem-pop PTFE			30–75[a]	

[a] Secondary patency.
Fem, femoral; occl., occlusion; pop, popliteal; PTA, percutaneous transluminal angioplasty; PTFE, polytetrafluoroethylene.
Source: Data from Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II).

increasing length of a lesion there is an increasing risk of early reocclusion. Stenting appears to improve patency, at least for longer lesions (Table 52.1) [15]. When the indication for PTA is claudication, patency is better than if the indication is critical ischaemia. This difference relates to the more extensive nature of the disease in critical limb ischaemia (poor run-off vessels). The three-year patency is 48%, which may be improved to 64% if stenting is added. In critical limb ischaemia, the results at three years show a patency of 30% without stenting and 63% with stenting (Table 52.1) [15]. PTA of crural vessels is also feasible; however, the long-term results are not good. Data on limb salvage with PTA of crural vessels alone are still scarce, despite these procedures having been developed extensively in the last five years. Dual-antiplatelet therapy may be used after endovascular therapy, although guidelines recommend either dual or monotherapy [16]. Recently dual-pathway inhibition by low-dose rivaroxaban and aspirin has been shown to reduce major adverse cardiovascular and limb events in individuals with peripheral arterial disease undergoing revascularization [13].

Open surgical revascularization

Open surgical revascularization and PTA are both used similarly for treatment of critical limb ischaemia, but for longer lesions (>20–25 cm) many clinicians prefer bypass surgery using autologous vein grafting [16]. For claudication, open surgical treatment is rarely performed, whereas for extensive disease of the distal aorta and iliac arteries, the aorto-bifemoral bypass may still be performed because it is the procedure with the best long-term outcome. However, PTA is by far the dominant therapy and endarterectomy of the femoral artery, as described in what follows, may also be an option for treatment of claudication. Only one trial, the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial, has compared open surgery with endovascular treatment of critical limb ischaemia [17]. The primary efficacy outcome measure was amputation-free survival, but because approximately two-thirds of the endpoints were deaths, only one-third of the endpoints really determined which procedure was best. Within six months postoperatively there was no difference in the primary endpoint, but thereafter bypass individuals seemed to do better [17]. The Best endovascular vs. Best surgical therapy in individuals with Critical Limb Ischemia (BEST-CLI) trial has randomized and treated almost 2000 individuals with either PTA or bypass surgery; results are anxiously awaited.

In general, two surgical techniques are used: endarterectomy and bypass. Endarterectomy is performed by separating the intima from the media, and in this manner the atherosclerotic lesion can be removed. Endarterectomy can be used in cases with severe occlusive lesions of limited anatomical extension in the external iliac or in the common femoral artery. The advantage of this technique is that it can often be performed without the use of artificial graft material and patency is excellent. Bypass is preferred when the obstructive and/or occlusive lesions are extensive (e.g. total superficial femoral artery occlusion or multiple serial lesions warranting a femoral–crural bypass; Figure 52.4). Bypass surgery can be performed with artificial materials or with autologous veins. For bypass of aortic or iliac artery origin, artificial grafts are almost always used. This is because there is no easily removable vein with similar dimensions that can be used in these locations. Dacron or polytetrafluoroethylene (PTFE) grafts perform very well in the aorto–iliac–femoral region. For peripheral bypasses, typically originating from the common femoral artery, autologous vein grafts are preferred for two reasons: they last longer (much better patency;

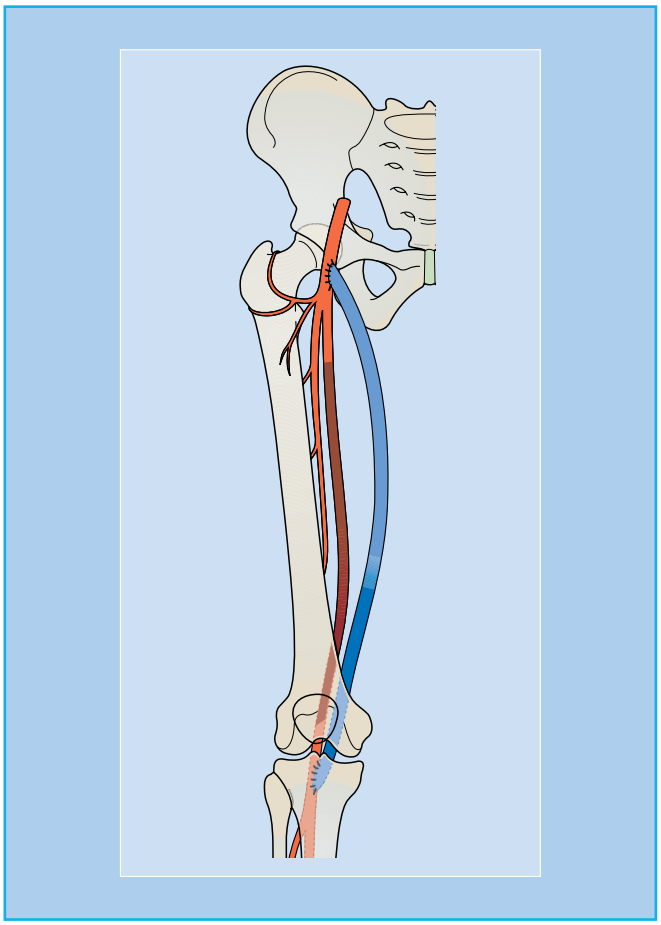


Figure 52.4 Long superficial femoral artery occlusion treated with femoro-popliteal bypass.

Table 52.1) and they carry less risk of infection. For longer bypasses, such as from the common femoral to the popliteal artery below the knee, a saphenous bypass is performed, leaving the vein *in situ*. This means that the vein is left in its original anatomical location; however, the proximal and distal ends are anatomized to the arterial system. The venous valves are cut with a knife mounted on a catheter and side branches are occluded. In this manner, the vein retains its nervous innervations and native vascularization.

Complications of endovascular treatment

Complications relate mainly to the site of puncture and the risk of peripheral embolization. *Systemic* cardiovascular complications are rare. Haematoma in the groin access point is common; however, it only rarely requires any action to be taken. Development of an iatrogenic pseudo-aneurysm is seen in 0.5–1% of cases and can easily be treated with ultrasound-guided compression or ultrasound-guided thrombin injection.

Complications of open surgical treatment

Complications can be divided into local and systemic categories. The former relate to the actual incisions and dissections, including wound healing and infections. Whereas complications from accidental damage to other organs and/or structures are very rare, wound-healing problems and infections are unfortunately fairly common. In particular, surgery on the lower limb involving the groin and peripheral incisions have wound complications in 10–20% of cases (e.g. haematoma, lymph oozing, or necrosis of the wound) [18]. Infections are seen in 3–5% of cases, approximately one-third involving the vascular reconstruction. Infection of the vascular reconstruction is more frequent when using artificial graft material [18].

Systemic complications to open surgical revascularization relate to the surgical trauma and to the stress response. In vascular reconstructions involving the aorta and other central arteries, the cardiopulmonary complication rate is considerable. Implantation of an aorto-bifemoral bypass graft is associated with a 30-day mortality of 2–5% and a rate of *general* complications of 10–15% (e.g. pulmonary, cardiac, renal, prolonged stay in the intensive care unit, and stroke) [18]. Systemic complications to peripheral revascularizations occur less frequently; nevertheless, they are considerable. When the indication is claudication, the morbidity with respect to general complications is low, 2–4%; however, in cases of critical ischaemia and peripheral bypass surgery, the morbidity increases to 10%, with a 30-day mortality of 3–5%. This difference in morbidity reflects the more advanced generalized atherosclerotic disease in individuals with critical ischaemia. In people with diabetes, complications are more common, especially with open surgery. A doubling of risk should be expected.

Results of endovascular and open surgical reconstructions

Results of reconstructions are summarized in Table 52.1. In general, when treating more centrally located arterial obstruction, the long-term results are better. In addition, treating people with claudication results in better long-term outcomes than operating on those with limb-threatening ischaemia. This difference relates to the generally poorer condition of the peripheral circulation in cases of critical ischaemia, with better run-off vessels in the person with claudication.

Vein grafts perform better in peripheral reconstructions. It may seem unrewarding to treat people with critical limb ischaemia with a peripheral bypass using an artificial graft when there is only a 50% chance of its being patent at one year; however, if the alternative is amputation and/or very poor quality of life (i.e. severe rest pain), one year with a functioning graft may very well be worthwhile for both the individual and the surgeon. Limb salvage as a result of revascularization is almost always better than patency of the reconstruction, because in many cases, once the ischaemic limbs with tissue loss have healed, the *need* for amputation becomes less. This is because wound healing increases the needed blood supply, but once wounds are healed, resting blood flow needs are less. People with diabetes typically have poorer outcome of vascular reconstructions, with patency rates that are inferior to those in individuals without diabetes. People with diabetes have more complications to treatment; not only infections but also systemic complications are more common.

Acute lower-limb ischaemia

Acute lower-limb ischaemia is most often caused by thrombosis in existing atherosclerosis (i.e. a person with previous symptoms of chronic peripheral arterial disease). Another common cause is thrombosis of a popliteal aneurysm. Embolism remains a further common cause, although not as often as in the past because of better anticoagulant therapy for people with atrial fibrillation. Around 80% of emboli are of cardiac origin; however, aneurysms of the aorta or peripheral aneurysms as well as atherosclerosis in a proximal artery may give rise to peripheral emboli.

Other causes include trauma and iatrogenic lesions (e.g. from arteriography with puncture of the femoral artery). Aortic dissection may cause lower-limb ischaemia and also acute deep venous thrombosis (phlegmasia cerulea dolens). The incidence of acute limb ischaemia in Western Europe is 300–400 per million per year.

Pathophysiology

Thrombosis is caused by plaque rupture and subsequent thrombosis. Distal to the acute occlusion, arterial flow is slow and, when combined with a hypercoagulable condition, it may lead to further thrombosis. The degree of ischaemia depends on the location and degree of collateral development. Therefore, thrombosis is often better tolerated than embolism because people with existing atherosclerosis most often have developed collaterals.

Emboli will typically occlude an artery at a bifurcation: in the lower limbs, at the aortic bifurcation (saddle embolus), iliac artery, and femoral artery bifurcation. Around 60% of cardiac emboli will end in the lower limbs, 15% in the arms, and the rest in the brain and other organs. Microemboli, typically from aneurysms, affect small peripheral arteries, and are therefore the cause of *blue toe syndrome*.

Symptoms

Acute ischaemia is characterized by pallor, pain, pulselessness, paraesthesia, and paresis (the *5 Ps*). Symptoms may begin dramatically and in some cases the late signs of ischaemia, paraesthesia, and paresis occur within a few hours. More often, symptoms begin with pain and paraesthesia and later sensory and muscular paresis. Acute ischaemia is traditionally divided into three classes: viable, threatened, and irreversible (Table 52.2).

Diagnosis

Diagnosis is often easy with typical clinical signs. ABI will be low, if measurable at all. Individuals with a history of intermittent claudication in the affected limb will probably have suffered thrombosis in the stenotic/affected arterial region. Imaging with either duplex

Table 52.2 Separation of threatened from viable extremities.

		Findings		Doppler signals	
Category	**Description/prognosis**	**Sensory loss**	**Muscle weakness**	**Arterial**	**Venous**
Viable/threatened	Not immediately threatened	None	None	Audible	Audible
a. Marginal	Salvageable if promptly treated	Minimal (toes) or none	None	(Often) inaudible	Audible
b. Immediate	Salvageable with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	(Usually) inaudible	Audible
Irreversible	Major tissue loss or permanent nerve damage inevitable	Profound, aesthetic	Profound, paralysis (rigour)	Inaudible	Inaudible

ultrasound, magnetic resonance angiography (MRA), computed tomography angiography (CTA), or digital subtraction angiography (DSA) is possible, but may delay treatment. In cases of thrombosis, it is most often desirable to perform arteriography with subsequent thrombolysis in order to visualize the underlying pathology causing the thrombosis.

Prognosis

If revascularization is possible before irreversible ischaemia has occurred, the limb can be salvaged and normal function regained. Comorbidity is high in cases of acute ischaemia; when acute revascularization is needed, outcomes after hospitalization are poor, with ~15% disabled or dead [19]. This is due to release of toxic substances from ischaemic tissue combined with existing severe cardiovascular atherosclerotic disease.

Treatment

Thrombosis in existing atherosclerotic lesions may be treated by endovascular or open surgery. The former is preferred if revascularization is not imminent. By catheter-directed intra-arterial thrombolysis, the underlying atherosclerotic lesions will be exposed and may in some cases be treated by PTA and/or stenting. In other cases, bypass surgery may be needed. Inoperable cases may be converted into operable cases by thrombolysis, because distal thrombosis most often makes surgery (and PTA) useless when there are no run-off vessels. Another advantage of thrombolysis is that emergency surgery is converted into a less urgent intervention. Emboli can be treated by embolectomy by inserting a balloon catheter, in either the femoral or popliteal artery, and retracting the emboli after inflating the balloon (Figure 52.5). Some cases of embolism may also be treated by thrombolysis.

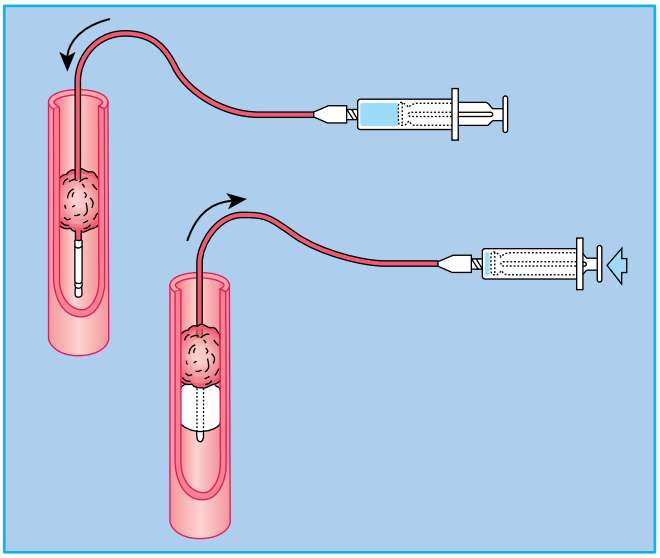


Figure 52.5 Embolectomy performed with a balloon catheter.

Prevention

Arterial emboli have a high recurrence rate and the underlying case should be treated, if possible, with corrective treatment for atrial fibrillation and resection or exclusion of aneurysms. If the source of embolism cannot be eliminated, anticoagulation must be considered.

Atherosclerosis of renal and mesenteric arteries

Renal artery obstruction

Renal artery obstruction can cause severe hypertension and renal failure, but interventional treatment may improve both conditions. Today, open surgical management is only rarely performed, because endovascular management is much less invasive and is feasible in the majority of cases. Open surgery, thromboendarterectomy or bypass, is performed when renal artery disease is combined with other pathology such as aortic occlusion or abdominal aortic aneurysms.

However, the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) study showed that renal artery revascularization (stenting) of atherosclerotic lesions in order to treat renovascular hypertension is in general not better than optimal medical therapy [20]. This was surprising and has reduced the use of this intervention, and so it is now mainly indicated for renal artery stenosis due to fibro-muscular dysplasia. There may be rare cases where revascularization is performed to improve renal function; however, this is done against an empirical background.

Mesenteric artery occlusive disease

Mesenteric artery occlusive disease may cause abdominal angina. Just like atherosclerotic lesions in other locations, many cases are asymptomatic and probably do not need intervention with regard to the obstructive disease, but lifestyle changes and medical preventive treatment are indicated. Individuals with classic symptoms, post-prandial pain occurring 10–20 minutes after a meal in addition to weight loss, often benefit from revascularization. However, many individuals have less obvious symptoms, and the mere occurrence of a lesion on one of the three main vessels supplying blood to

the gastrointestinal tract (coeliac trunk and superior and inferior mesenteric arteries) does not warrant interventional treatment. In general, a single lesion in one of the three arteries is seldom thought to cause ischaemia. Diagnosis is possible by ultrasound of the suprarenal vessels in most cases, otherwise CTA, MRA, or DSA may be needed. Interventional treatment is mainly balloon angioplasty and stenting. Long occlusions of the superior mesenteric artery and/or occlusive mesenteric disease combined with other pathology of the aorta may be treated by open surgery (e.g. aorto-mesenteric bypass or transposition).

Ischaemia of the arm

Atherosclerosis and ischaemia of the arm are much less common than in the lower limb. The most common location for development of atherosclerosis in the arteries supplying the upper extremity is in the brachiocephalic trunk and subclavian arteries central for the origin of the vertebral arteries. Rarely, occlusive lesions are located more peripherally in the subclavian or axillary arteries. Takayasu vasculitis may also cause upper extremity ischaemia.

Typical symptoms of chronic arm ischaemia

Symptoms include claudication. In typical cases, pain is encountered when performing tasks with the arms elevated, such as hanging laundry, or other physical use of the arm. Critical ischaemia with rest pain or gangrene is rare, but may occur. Diagnosis is easy, with lack of pulses at palpation. Measurement of bilateral blood pressure may show a difference and ultrasound may locate and quantitate the stenotic lesion. If blood pressure cannot be measured by auscultation, a Doppler device may be used as for measurement of ankle blood pressure. Additionally, or in case of severe ischaemia, finger pressure measurement by the strain gauge technique may be used. Upper-arm angiography by CTA, MRA, or DSA may be supplemental.

The prognosis is often good, because development of critical ischaemia and the necessity for amputation are rare. Individuals with finger gangrene should be investigated for vasculitis.

Treatment of upper-extremity atherosclerosis is similar to that of atherosclerosis in other vascular distributions: risk factor reduction by lifestyle changes and preventive medications for all, and revascularization in some. In fact, only rarely is interventional treatment indicated, but in cases of incapacitating functional pain and/or critical ischaemia, revascularization should be considered. Endovascular treatment dominates because of its less invasive nature for lesions near the origin of the brachiocephalic trunk and subclavian arteries. For lesions that cannot be treated by endovascular techniques, such as long lesions or lesions that cannot be crossed by a guide wire, bypass surgery is indicated (carotid–subclavian bypass). Peripheral bypass of the upper extremity (e.g. at the level of the brachial artery) is rare and patency is poor.

Acute arm ischaemia

Acute arm ischaemia is most often caused by embolization, but alternatively can be caused by thrombosis in an existing stenosis, such as of the subclavian artery. Whereas the former may be treated easily by embolectomy via a small incision in the cubital fossa, the latter may be more complex to treat, perhaps requiring intra-arterial thrombolysis before vascular reconstruction. Embolism is most often of cardiac origin, from either atrial fibrillation, mural thrombus in the heart, or valve disease. Vascular causes include a subclavian aneurysm or stenosis. Microemboli may occur peripherally and present as gangrene of one or more fingers. Extravascular causes include a cervical rib. Obviously, eradication of the embolic source is crucial, if possible. Treatment of peripheral ischaemia may include thrombolysis, but in most cases collaterals develop and amputation does not become necessary.

Aortic aneurysmal disease (abdominal aortic aneurysm)

This section focuses on abdominal aortic aneurysms, because thoracic aortic aneurysms are not considered part of peripheral vascular disease. The main difference between individuals with and without diabetes with respect to treatment of aneurysms is that those with diabetes are more prone to complications after surgery; however, because of the nature of preventive surgery for aneurysms, this only rarely causes changes in management once the risk of surgery has been weighed against non-surgical treatment.

Aneurysm of the aorta is a common condition in older people, especially in the infrarenal aorta. An artery by definition becomes aneurysmal when the diameter locally increases by more than 50% compared with the *normal* diameter proximal or distal to this site. In cases of infrarenal aorta, an aneurysm is present when the diameter exceeds 30 mm.

The prevalence of abdominal aortic aneurysm is ~5% in men over 70 years of age; however, only a minority of them will have a size that mandates surgery (diameter >5–6 cm). In individuals with other atherosclerotic manifestations, such as peripheral arterial disease or carotid disease, the incidence of abdominal aortic aneurysms is 2–3 times greater. There is a 2 : 1 ratio of aortic aneurysms occurring in men to women. Finally, the tendency to develop abdominal aortic aneurysms is partly inherited, as the risk for a man with a father or brother with aortic aneurysm is ~20%. People with diabetes seem to have a slightly lower incidence of abdominal aortic aneurysm, ~80% of those without diabetes [21].

Pathophysiology

Arteries enlarge with age, and the diameter of the infrarenal aorta is normally <20 mm in a 70-year-old man. If the wall weakens locally, an aneurysm develops. A true aneurysm develops when all three layers in the arterial wall are involved and dilate, as in the case of the typical infrarenal aortic aneurysm. False aneurysms or pseudo-aneurysms develop after iatrogenic trauma, such as PTA or other transfemoral procedures, and at arterial anastomotic sites. Finally, dissection occurs when a rupture of the intima allows blood to enter between the layers of the artery wall.

Aortic aneurysms may rupture, almost certainly leading to death. It is estimated that 80–90% of all individuals with ruptured aneurysms die before they get to hospital. Ruptured aneurysms cause an estimated 2–3% of all deaths among men, whereas the proportion for women is 1%.

In most abdominal aortic aneurysms, there is an atherosclerotic degeneration of the vessel wall that dilates; however, it is unclear why atherosclerosis in some people results in occlusive disease and in others in aneurysm development. Accelerated breakdown of elastin has a role in aneurysm development. The simultaneous presence of both occlusive and aneurysmal disease is common in many individuals. Inflammatory aneurysms are present in 5–10% of aortic aneurysms where the aortic wall is thickened as part of peri-aneurysmal or retroperitoneal fibrosis.

Symptoms from abdominal aortic aneurysms

Symptoms are rare and most are asymptomatic. Diagnosis is often made coincidentally, such as when a person complains of slight

upper gastric pain and has an ultrasound of the gallbladder, which discloses the aortic aneurysm. Also, typically the individual may complain of back pain and have a lumbar X-ray. Whether the pain is really related to the abdominal aortic aneurysm, to gallstones, or to the back is often difficult to ascertain.

Some individuals will sense a pulsation in the abdomen, while large aneurysms may cause discomfort or compress surrounding organs, mainly the gastrointestinal tract. The main risk is rupture, which, when intraperitoneal, most often leads to immediate death. If rupture is into the retroperitoneal space, a haematoma may be contained and the person may survive for hours. Rupture and development of a haematoma lead to pain in the abdomen and/or back. Chronic rupture is rare, because almost all cases will be fatal within hours. Aneurysms may cause peripheral embolization, resulting in a cyanotic or gangrenous toe as the first symptom.

Diagnosis

Diagnosis is easy, as ultrasound is very accurate in making the diagnosis and estimating the diameter of the aneurysm (Figure 52.6). In the few cases where ultrasound is inconclusive, a primary computed tomography (CT) scan may be necessary. Otherwise, CT or magnetic resonance (MR) scanning is only performed when the size of the aneurysm dictates that intervention should be considered (aortic diameter of >5 cm). Arteriography is rarely performed for abdominal aortic aneurysm; however, in cases of both abdominal aortic aneurysm and symptoms of peripheral arterial disease, an arteriogram may be warranted for planning of the revascularization procedure (CTA). Anyone with acute abdominal pain in pre-shock should always be suspected of ruptured abdominal aortic aneurysm.

Prognosis

The risk of rupture is related to the size of the aneurysm. When the diameter exceeds 6 cm, the annual risk of rupture is 10–20%, whereas the risk of rupture in the case of an aortic aneurysm with a diameter of 3–4 cm is <1%. Aneurysms tend to expand; small aneurysms dilate by 1–2 mm/yr, whereas larger aneurysms may expand 2–3 times faster. Smoking and hypertension seem to increase the rate of growth. Rupture is associated with 90% mortality, but the survival for those who reach hospital and have immediate surgery is ~50–60%. Concomitant coronary disease is responsible for a 50–100% increased mortality of individuals with aneurysms even when aneurysm mortality is disregarded.

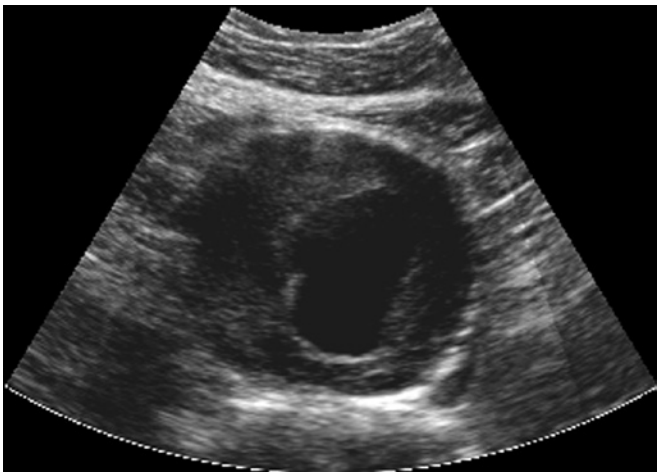


Figure 52.6 Ultrasound image of an abdominal aortic aneurysm. Note the presence of a large thrombus inside the aneurysm sac.

Treatment

Treatment of abdominal aortic aneurysms involves, in addition to surgery for some, the same preventive treatment as is given to other people with atherosclerotic manifestations: lifestyle changes and medical therapy with platelet inhibitors, statins, and blood pressure control.

Treatment of a ruptured aortic aneurysm is always interventional (open surgical or endovascular), unless the overall condition is considered too poor to attempt rescue. In some cases, a fatal aortic aneurysm may be a dignified death, for example in an older person with end-stage renal or heart failure. Symptomatic non-ruptured aneurysms should be treated acutely or subacutely because of the risk of imminent rupture.

Treatment of a large asymptomatic abdominal aortic aneurysm reduces mortality [22], and those with an asymptomatic aneurysm should be offered elective interventional treatment if the risk of rupture exceeds the risk of the procedure, and if the person is fit for the procedure and expected to have good-quality years remaining. Because any procedure for treatment of aortic aneurysm either carries a considerable perioperative risk or involves a very long postoperative period with potential reinterventions, the decision to offer interventional treatment is not always easy, and a decision should be taken in consultation with the individual and their family.

The choice between treatment modalities is made keeping the following facts in mind.

Open surgical treatment with resection of the aneurysm and replacement of the diseased part of aorta with an artificial graft has been performed for ~50 years (Figure 52.7). It is a well-proven procedure with known risks and long-term results, including an overall 3–5% perioperative mortality, but limited aneurysm morbidity after the procedure. Complications of open surgical repair relate to the considerable surgical trauma of this major procedure. Around 10–20% of individuals will develop general complications such as cardiac, pulmonary, and renal complications, in addition to requiring a prolonged stay in the intensive care unit and stroke.

Endovascular aneurysm repair (EVAR) involves inserting a collapsed prosthesis via the femoral artery, placing it below the renal arteries, and deploying and fixing it (stenting) under X-ray guidance. The technique mostly used today involves inserting a bifurcated graft from one femoral artery and then placing the other limb via the contralateral femoral artery (Figure 52.8). EVAR has lower perioperative morbidity: 1.5% compared with 4.5% for open surgery [23–26]. There are few complications to EVAR in the perioperative period, but a considerable number of individuals will need repeat interventions, which in most cases can be performed by endovascular techniques. These include placement of another proximal stent because of endo-leak (blood re-entering the excluded aneurysm sac, which is thereby again at risk of rupture) and embolization of inferior mesenteric or internal iliac arteries. Because the long-term results of EVAR are not well known (>10 years), continuous surveillance with annual CT or ultrasound scans is necessary. Until a few years ago, the number of repeat interventions because of either migration or failure of the implanted device, both leading to endo-leak were considerable; however, more recent data show improvement to 10–15% at three years [25].

As an example of choice of treatment modality, a 65-year-old man with a 6 cm aneurysm and no other known comorbidity should be offered treatment, preferentially open surgery, because

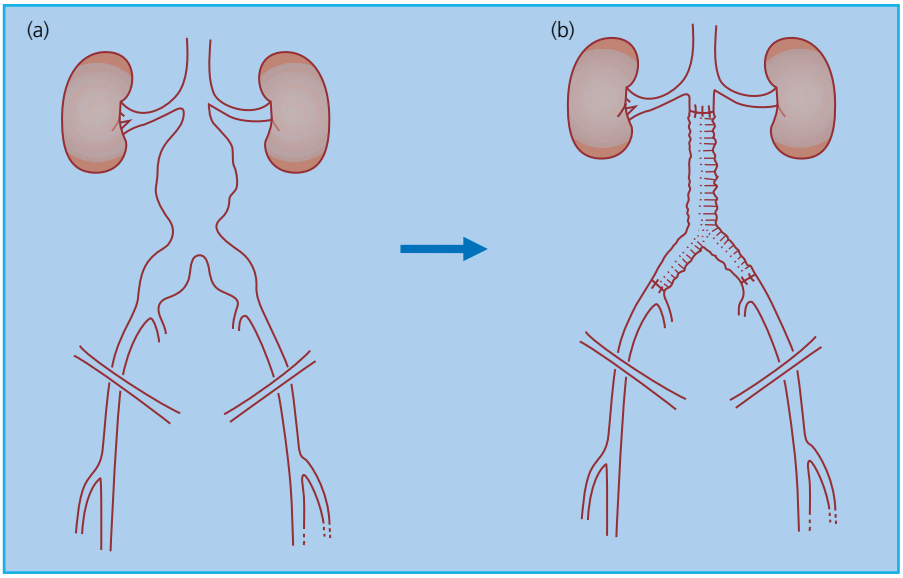


Figure 52.7 (a, b) Abdominal aortic aneurysm treated by resection and implantation of an aorto-bi-iliac bypass graft.

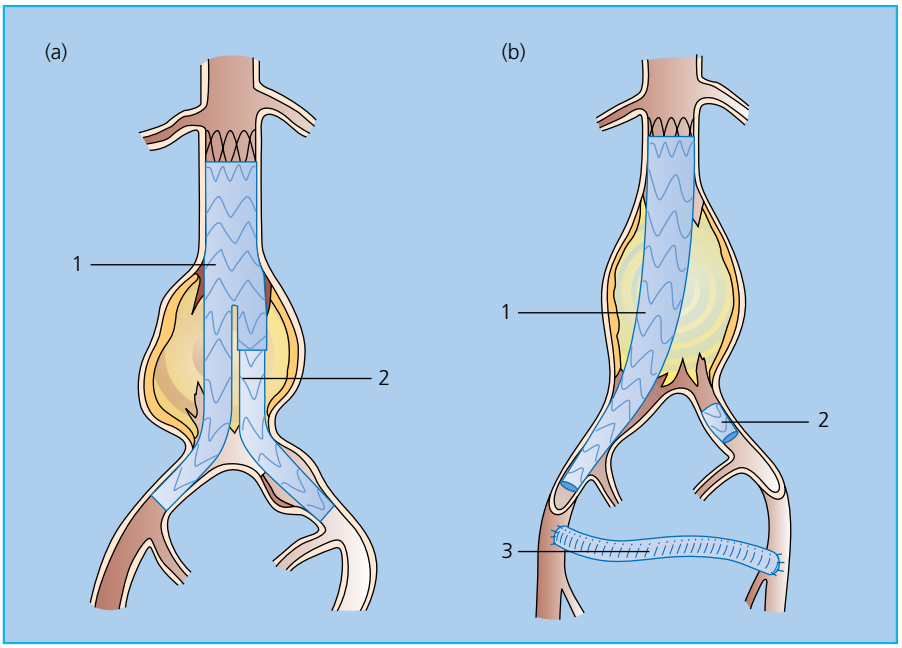


Figure 52.8 Abdominal aortic aneurysm treated by endovascular repair. (a) First the bifurcated graft (1) is inserted via the right femoral artery and fixed by stenting at the proximal and distal end of the graft. The left limb (2) is inserted via the left femoral artery and connected to the main graft. (b) Insertion of an aorto-uni-iliac endograft (1) combined with a femoro-femoral bypass graft (3) is used when one of the iliac arteries (2) cannot be passed.

his perioperative risk will be low (2–3%), whereas the annual risk of rupture is ~10%. At the other end of the spectrum is the 80-year-old man with previous coronary artery bypass graft surgery and a similar-sized aneurysm of 6 cm. His risk with open surgery includes >10% 30-day mortality in addition to a considerable risk of other complications. Endovascular treatment could be a good alternative for this man if he is expected to live at least 3–5 years.

EVAR has been considered to be a treatment alternative for individuals unfit for open surgery. The EVAR-2 trial tested this hypothesis and participants found to be unfit for open repair were randomized to either conservative management or EVAR. Survival was not improved by EVAR and it was poor in both groups: ~50% of participants in both groups were dead at three years and only one-quarter of deaths were aneurysm related [26]. Hence being found unfit for surgery in this study indicated a poor prognosis in general that EVAR did not affect.

The most recent European guidelines recommend EVAR for most cases now, but it is always a matter of discussion between clinician and person with the aneurysm, so that the advantages and disadvantages of both techniques are clear to the individual. In cases of ruptured abdominal aortic aneurysm EVAR is recommended if possible [27].

Screening

The value of population-based screening for abdominal aortic aneurysms is now well documented. A meta-analysis of four randomized controlled trials found aneurysm-related mortality to be reduced by 43% in those offered screening [28]. Today, it is recommended in many countries that men >65 years and previous smokers undergo ultrasound screening. Family members who are direct descendants and siblings of those with aortic aneurysms should also undergo screening.

Peripheral aneurysms

Aneurysms may develop at other locations, the popliteal and femoral arteries being the second and third most common locations. More than 50% of individuals with peripheral aneurysms also have an aortic aneurysm. Symptoms are different in the sense that rupture is less common; however, symptoms derived from compression (popliteal vein thrombosis, pain, and other symptoms of nerve compression), peripheral embolization, or thrombosis of the aneurysm most often bring the individual to medical attention.

Treatment is the same as for aortic aneurysms: general prevention against atherosclerotic disease and intervention in symptomatic cases. Popliteal aneurysms are generally treated surgically by exclusion and bypass or by resection and replacement by a short graft. Femoral aneurysms are treated by resection and placement of a graft. Endovascular management is possible; however, graft thrombosis and failure of stent graft material have so far made indications unclear. Large asymptomatic peripheral aneurysms should probably be treated by either open or endovascular surgery, although no documentation is currently available that such treatment is beneficial.

Aneurysms of visceral or renal arteries may occur but are rare. Treatment is interventional when they are large. Endovascular management is under development, but its indications are not yet settled.

Carotid artery disease

This section focuses on stroke and carotid disease, while Chapter 51 addresses cerebrovascular disease in general, including pathophysiology and symptoms. The relationship to atherosclerosis for many people with stroke is well documented, although stroke, unlike other ischaemic conditions, has other common pathogenetic mechanisms.

It is very important to discriminate between symptomatic disease and asymptomatic cases. People with recent cerebrovascular symptoms and an ipsilateral stenosis are comparable to those with a recent acute coronary event: the risk for a new thromboembolic event is very high and diagnostic work-up and treatment should be started immediately. The pathogenetic mechanism is similar to that of an acute coronary event with plaque rupture and subsequent thrombosis; however, in the case of the carotid, embolization into a cerebral artery is much more common than thrombotic occlusion of the carotid artery itself. Perhaps the larger diameter of the carotid artery explains this difference.

The prevalence of carotid stenosis is high. Among people with acute cerebrovascular symptoms, an ipsilateral stenosis of >50% diameter reduction is found in 15–20% of cases. In people with other clinical atherosclerotic manifestations, a carotid stenosis is found in 20–30%.

Prognosis

The risk of stroke is increased in the presence of carotid stenosis. For asymptomatic people with a carotid stenosis exceeding 60% diameter reduction, the annual risk of ipsilateral stroke is ~1% with optimal medical prevention (anti-atherosclerotic treatment). When carotid stenosis is related to recent ipsilateral cerebral ischaemic symptoms (symptomatic stenosis), the risk is much higher, especially just after the first event. The 30-day risk of stroke in people with previous cerebrovascular symptoms is as high as 10% when an ipsilateral carotid stenosis is present. Thereafter, the risk gradually declines and after one year it is ~2–3% annually, almost similar to asymptomatic carotid stenosis. The three-year risk of ipsilateral stroke is 15–30% in symptomatic individuals with a stenosis >70% diameter reduction.

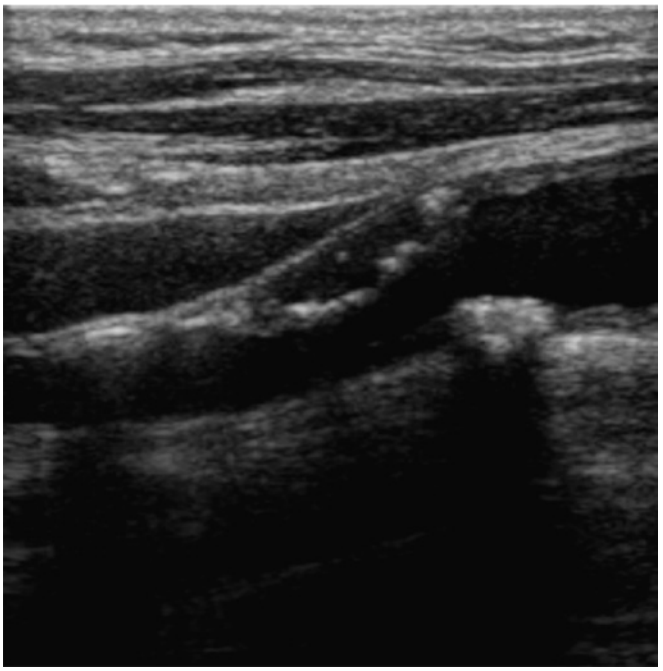


Figure 52.9 B-mode ultrasound image of carotid stenosis. The top part is echolucent, indicating a high content of lipid/necrotic core; the bottom part is echogenic, indicating a fibrous plaque.

Diagnosis

Diagnosis of carotid disease should be carried out by duplex ultrasound scanning (Figure 52.9). The accuracy of the method is well documented for both identification and quantification of degree of stenosis. Many surgeons will perform carotid endarterectomy based only on ultrasound examination.

Treatment

Treatment of people with carotid stenosis is like that of any other condition related to atherosclerosis: treatment of the atherosclerotic disease itself and treatment of local manifestations. Risk factor reduction, including changes in health behaviours, is exactly the same as for individuals with other clinical manifestations of atherosclerosis, although there may be regional variation in the choice of antiplatelet agents. Aggressive lipid lowering reduces both the risk of recurrent stroke and the risk of coronary events, especially in this group of individuals [29–31].

It is important to realize that any invasive treatment for carotid stenosis is performed to prevent future *local* events (stroke). Hence the risk of the intervention itself should be weighed against the absolute risk of an event. Furthermore, the most common complication of surgery and stenting is ipsilateral stroke, the event that the procedure is supposed to prevent. Most importantly, the overall risk to the individual (including that of other conditions) should be weighed against the absolute risk reduction derived from the procedure.

Symptomatic carotid stenosis

Symptomatic individuals with carotid stenosis benefit from endarterectomy when the stenosis is >50–70% diameter reduction and neurological symptoms are within six months of surgery [32, 33].

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and European Carotid Surgery Trialist's Collaborative Group (ECST) trial [32, 33] randomized simultaneously, but independently, symptomatic individuals with carotid stenosis to best medical treatment or best medical treatment plus endarterectomy. Both trials showed significant benefit (50% relative risk reduction) in those with stenosis >70% diameter reduction, whereas in the group with 50–69% stenosis there was only a marginal effect, and in participants with stenoses <50% there was no benefit.

Subsequent reanalysis of the pooled data from these two trials, however, showed that the time interval between onset of neurological symptoms and surgery was the most important predictive factor of benefit for the individual [34]. In general, the earlier an operation is executed, the greater is the benefit. The overall absolute risk reduction of ~15% conveyed by endarterectomy could be doubled when individuals received surgery within two weeks of symptoms (number needed to treat to prevent one stroke = 3). With the knowledge gained during the last 10–15 years concerning vulnerable plaques and plaque rupture, this finding does not come as a great surprise; however, when these trials were designed, this pathogenetic mechanism of acute ischaemia was unknown.

Male sex, older age, and greater severity of stenosis all increase the risk of future stroke in people with stenosis without any increased risk of the surgical procedure, hence the overall benefit is greater [34]. In addition, imaging parameters seen on ultrasound, MR, and CT scans further increase the risk of future stroke and should be considered [35].

Asymptomatic carotid stenosis

Asymptomatic carotid stenosis is more controversial, although two major trials have shown a small but statistically significant benefit of surgery. First, the Asymptomatic Carotid Atherosclerosis Study (ACAS) trial showed a 50% relative risk reduction of ipsilateral stroke, but the absolute risk reduction was marginal, only 1% per year [36]. Later, the Asymptomatic Carotid Surgery Trial (ACST) reproduced these findings [37]. Taking into consideration that the average annual mortality during the trials was 3–4%, in addition to other ischaemic events that were unaffected by the procedure, it may be questioned whether the cost–benefit is reasonable both for the individual and for society. The medical treatment offered during these trials was much poorer than that recommended today; hence the outcomes of these trials may not be reflective of the risk in these individuals today. If or when better criteria for selection of individuals at higher risk become available, selective surgery for high-risk cases of asymptomatic carotid stenosis may yield greater or even much greater benefit.

Technical considerations

Technically, carotid endarterectomy may be performed in two ways: classic endarterectomy (Figure 52.10) or eversion endarterectomy. In the latter, the internal carotid artery is divided from the bifurcation, and endarterectomy is performed by everting the vessel wall, thereby removing the carotid lesion. After the stenosis has been removed, the bifurcation is reconstructed by reanastomosing the internal carotid to the bifurcation.

Carotid endarterectomy may be performed under general or local anaesthesia. Classically, general anaesthesia has been preferred; however, this has carried the challenge of monitoring cerebral circulation during clamping of the carotid artery. Various methods have been used, including electroencephalography, stump pressure, distal internal carotid artery pressure, evoked potentials, near-infrared spectroscopy, transcranial Doppler ultrasound, and more. None of these methods has proven ideal, and so some surgeons use a shunt on a selective basis, whenever their method for monitoring indicates risk of cerebral ischaemia during clamping, whereas others use a shunt routinely. By contrast, performing endarterectomy under local anaesthesia gives the surgeon the opportunity to communicate with the patient during clamping. Having the person awake and responsive during surgery may represent the best monitoring of cerebral function during clamping. Also, local anaesthesia may carry less cardiac and pulmonary risk. Smaller trials and a meta-analysis indicated superiority of local anaesthesia [38]; however, the later General Anaesthesia versus Local Anaesthesia for carotid surgery (GALA) trial reported its results after randomizing 3529 participants to either universal or local anaesthesia for carotid endarterectomy, and there was no difference in the risk of perioperative stroke or death [39].

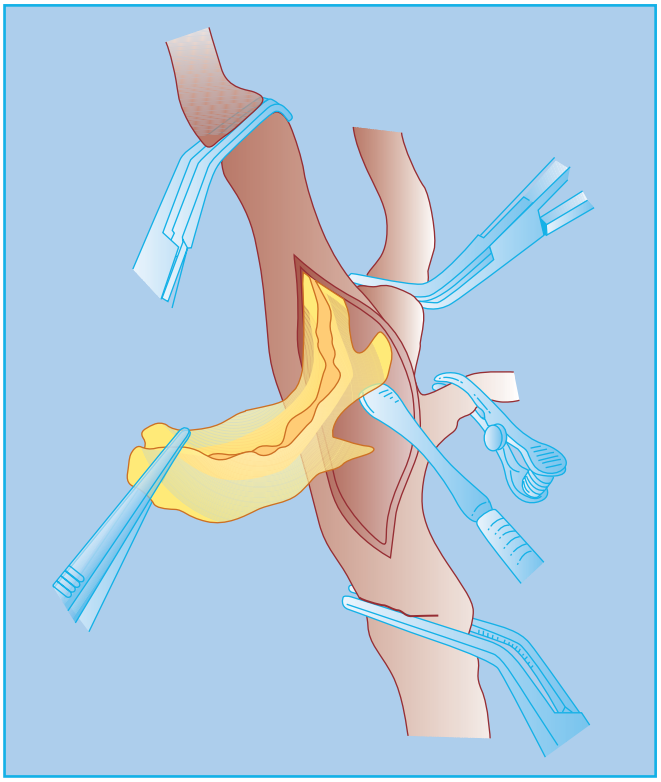


Figure 52.10 Carotid endarterectomy where the intima–media complex is dissected free of the adventitia and removed.

Carotid stenting

Carotid stenting has yet to be proven to prevent ipsilateral ischaemic events in randomized clinical trials. Seven randomized controlled trials comparing stenting with endarterectomy have been published; however, so far they have focused only on comparison of perioperative complications. The two most recent trials, Endarterectomy Versus Angioplasty in patients with Symptomatic Severe carotid Stenosis (EVA-3S) and Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE), failed to show an advantage of the less invasive carotid stenting method with respect to perioperative events [40, 41]. In fact, the EVA-3S trial was stopped early because of excess complications in the stenting group [40]. A Cochrane meta-analysis including all seven randomized controlled trials

favoured surgery with respect to the primary outcome of perioperative death and ipsilateral stroke [42]. Most recently, the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) showed equivalence of stenting and endarterectomy, but in a trial with a combined endpoint of death, stroke, and myocardial infarction, as detected by the increase in enzymes in individuals without any other symptoms. Accordingly, focusing on the risk of death and stroke, stenting was associated with more complications [43]. Nevertheless, it is important to acknowledge that technology develops rapidly and some of the trials may have used devices and/or technologies that are already outdated. Similarly, there may be differences in trial design, and criticism has been made specifically regarding the training of the investigators in some studies. Interestingly, stenting appears to be associated with higher complication rates when performed early after onset of neurological symptoms and in older people – the two strongest indications. Finally, one should keep in mind that stenting should be evaluated in long-term studies, and compared not only with endarterectomy, but also with medical therapy, which has improved dramatically in the last 10–20 years. However, the most recent Cochrane analysis still recommends endarterectomy over stenting for symptomatic carotid disease [44] in accordance with most recent guidelines [35].

It may be questioned whether the evidence for carotid endarterectomy is outdated. Three of the four major trials proving endarterectomy to be of value for symptomatic and asymptomatic surgery were performed when the only fairly constant preventive medication given was aspirin. The last randomized trial was 8–10 years ago, and only 30% of the participants were taking statins. It was stated in the design of these trials that hypertension and hypercholesterolaemia were treated when present; however, in that era the treatment goals for both hypertension and hypercholesterolaemia were much laxer than they are now. Also, new drugs have been introduced and their benefit documented since these trials initially randomized individuals (e.g. statins, newer antiplatelet agents, dual-antiplatelet therapy, and newer antihypertensive drugs). It may be speculated that if these drugs were used systematically, the risk in people with carotid stenosis would be much less, not least in those with vulnerable plaques. Therefore, new trials are needed to test how today's medical therapy compares with intervention and if the best medical therapy remains inferior to surgery or stenting. New trials are *not* unethical – it is unethical not to undertake new trials.

Carotid revascularization prior to coronary artery bypass surgery has been practised in some institutions whereas others have not found it useful. The potential advantage is avoiding cerebral ischaemia during the relative hypotension *on pump*; however, the complications of carotid revascularization have outweighed the gains, as evaluated by recent reviews.

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9 Other Complications of Diabetes

53 Foot Problems in People with Diabetes

Frank L. Bowling[1,2], Keeley J. Foley[1,2], and Andrew J.M. Boulton[1,2]

[1] Department of Medicine, University of Manchester and Manchester Royal Infirmary, Manchester, UK

[2] Miller School of Medicine, University of Miami, Miami, FL, USA

Key points

- Diabetes-related foot problems remain the commonest cause of hospital admissions among people with diabetes in high-income countries.
- There are estimated to be 60 000 active diabetes-related foot ulcers in UK at any one time.
- Up to 50% of older individuals with type 2 diabetes have risk factors for foot problems.
- The risk of death five years after an individual with diabetes has acquired a foot ulcer is 2.5 times higher than the risk for a person with diabetes who does not have a foot ulcer.
- Up to 85% of lower-limb amputations are preceded by foot ulcers.
- Mortality after diabetes-related amputation exceeds 70% at five years for all individuals with diabetes.
- All people with diabetes should be screened for risk of foot problems on an annual basis. Those with risk factors require regular podiatry, self-management education, and instruction in foot self-care.
- Most foot ulcers should heal if pressure is removed from the ulcer site, the arterial circulation is sufficient, and infection is managed and treated aggressively.
- Any individual with a warm, unilaterally swollen foot without ulceration should be presumed to have an acute Charcot neuroarthropathy until proved otherwise.

Diabetes-related foot disease is a global challenge. This chapter discusses all aspects of foot disease in people with diabetes, focusing particularly on diagnosis and management in the prevention of lower-limb amputation. The chapter is underpinned by high-quality evidence and recently updated recommendations developed by the International Working Group on the Diabetic Foot.

The most feared manifestation of diabetes-related foot disease is amputation and at any one time 2–4% of people with diabetes are likely to have an active foot ulcer, equating to 62 000 people in England, 1.2 million across Europe, and 8.4 million globally [1, 2]. People with diabetes in England are 23 times more to likely to have a leg, foot, or toe amputation [3]. Five-year mortality is 45%, 18%, and 55% for neuropathic, neuroischaemic, and ischaemic ulcers, respectively, on multivariate regression analysis, with only increasing age predicting shorter survival time [4]. Around 8 in every 10 000 will undergo a major amputation and ~18 out of 10 000 will undergo a minor amputation. The Vascular Society of Great Britain and Ireland defines a major amputation as above the level of the ankle joint and a minor amputation below [5]. There were 2515 major amputations and 6640 minor amputations carried out in England between 2015 and 2018. All types of diabetes-related foot ulcers are associated with high morbidity and mortality. The increased mortality appears to be independent of factors increasing ulcer risk, such as neuropathy and peripheral arterial disease, in individuals with established foot ulcers [2].

Foot ulcers do not occur spontaneously, but arise from a combination of factors that can be modified to reduce the risk of ulceration. The International Diabetes Federation focused on the diabetic foot throughout 2005 with a worldwide campaign to *put feet first*, highlighting that diabetes is the leading cause of non-traumatic lower-extremity amputation throughout the world [6].

Epidemiology and economic aspects of diabetes-related foot disease

The Global Burden of Disease Study in 2016 was the first study to provide an estimate of the number of individuals living with diabetes-related lower-extremity complications [7]. The study reported that 131 million people (1.8% of the global population) had a diabetes-related lower-extremity complication at the time of the study [8]. The 2015 prevalence data from the International Diabetes Federation estimated that, annually, foot ulcers develop in between 9 and 26 million people with diabetes worldwide [6]. Diabetes increases the risk of lower-extremity amputation by 10–20 times and is associated with half of all lower-limb amputations globally.

Health economics of diabetes-related foot disease

In the USA, the direct costs of treating diabetes-related foot complications exceed the treatment costs for many common cancers; $176 billion is spent annually on direct costs for diabetes care, with one-third of that expenditure related to lower-extremity complications [9]. *The Lancet* launched an issue focusing on the burden of diabetes-related foot disease, which was the first time any major non-specialist journal had specifically focused directly on the issue. However, major challenges still exist if we are to reduce amputations globally [10].

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Aetiopathogenesis of diabetes-related foot lesions

Diabetic neuropathy

Diabetic peripheral neuropathy affects up to 50% of people with diabetes and is a leading cause of lower-limb amputation and incapacitating neuropathic pain [11]. Diabetic peripheral neuropathy can be either painful or painless, which makes the diagnosis challenging (Chapter 45) [11]. The loss of protective sensation renders individuals vulnerable to trauma without awareness in the latter stages of diabetic peripheral neuropathy and is also associated with unsteadiness, resulting in an increased risk of falls [11]. Symptoms, if present, include neuropathic pain, which can be difficult for individuals to describe but may include burning or electric shock–type pain, stabbing or shooting sensations, all of which are worse at night, or negative symptoms such as numbness, tingling, or the feet *feel dead* [11].

Sensory loss

Diabetic peripheral neuropathy results in loss of sensory protection in the foot for 75–90% of all cases [12]. The power of clinical observation is highly relevant to people with diabetes-related foot ulcer, and anyone with a plantar ulcer who is able to walk without limping should be considered to have diabetic peripheral neuropathy [13]. Lack of pain serves to reduce individual awareness of the foot, subsequently increasing the risk of delayed healing of injuries and ulcerations, infection, and in turn amputation (Figure 53.1) [13]. Risk management is based on developing the visual perception of the foot, in the absence of perception of sensation, which can be realized through daily foot examinations to identify sites of injury and potential ulceration.

Figure 53.1 A typical non infected neuropathic plantar ulcer located under the 2nd metatarsal head, the 2nd digit is dorsally dislocated resulting in metatarsal head depression a *plunger effect*.

Peripheral sympathetic autonomic neuropathy

Peripheral sympathetic neuropathy presents with dry skin that is prone to cracking (fissures) and often accompanied by fissures around the heel [13]. These characteristics are caused by autonomic dysfunction, which reduces sweating and production of natural moisturizing factors in the skin [14]. In the absence of large-vessel obstructive peripheral vascular disease, arteriovenous (distended dorsal veins) shunting leads to a warm foot. The *high-risk* neuropathic foot typically presents with high arches, clawing of the toes, prominent metatarsal heads, and small muscle wasting (Figure 53.2) [13]. Callus is often present on the plantar aspect of the foot, which is generally under the first metatarsal head where foot pressures are highest [13].

Screening

Over 50% of individuals with type 2 diabetes show signs of diabetic peripheral neuropathy, which can be identified through a comprehensive assessment. Guidance can be located via the American Diabetes Association document 'The comprehensive diabetic foot assessment', which provides clarity on the structure and content of a robust assessment. The International Working Group on the Diabetic Foot has also issued recent guidelines [15]. A disciplined screening assessment is the key to a comprehensive foot exam, including history and clinical examination (Box 53.1).

Bedside screening tools for neuropathy

Current guidelines advocate the use of simple tests such as the 10 g monofilament, but unfortunately not all 10 g monofilaments generate 10 g of linear pressure. Furthermore, they become fatigued and wear out. The literature is unclear about the definitive sites determining ulcer risk; however, there are sites that are common, such as the plantar surface of the metatarsal heads and apices (pulp) of the great toe [16].

The VibraTip™ 128 Hz (McCallan Medical, Derby, UK) is a device comparable with the 10 g monofilament and therefore could be considered a useful tool for screening for peripheral sensory neuropathy. Both the VibraTip and the Ipswich Touch Test are reliable and sensitive tests for identifying the high-risk foot [13].

Figure 53.2 The high-risk neuropathic diabetic foot demonstrating high arch, prominent metatarsal heads, clawing of toes, and callus under first metatarsal head.

Box 53.1 Salient features of a structured foot examination

History
Ulcer past or present
Minor or major amputation
Past or present neuropathic symptoms
Bypass surgery or angioplasty, intermittent claudication
Other diabetes complications:
- Visual impairment
- End-stage renal failure (on dialysis or post-transplant)

Social factors, living alone, smoking

Clinical examination
Skin temperature, insensate, unilateral warm foot with intact skin
Evidence of a Charcot foot
Anhidrosis (reduced sweating), fissure (cracks)
Soft tissue loss (ulceration)
Bacterial/fungal infections
Alteration in shape, prominent metatarsal heads
Footwear suitability

Peripheral arterial disease

Although peripheral arterial disease is described in detail in Chapter 52, brief mention of its role in the genesis of foot ulcers is necessary here. Peripheral arterial disease tends to occur at a younger age in people with diabetes and is more likely to involve distal vessels. Peripheral arterial disease is a major contributory factor in the pathogenesis of foot ulceration and subsequent major amputations. Peripheral arterial disease in isolation rarely causes ulceration; it is the combination of risk factors with minor trauma that ultimately leads to ulceration (Figure 53.3). Thus, minor injury and subsequent infection increase the demand for blood supply beyond the circulatory capacity and ischaemic ulceration and the risk of amputation ensue. In recent years, neuroischaemic ulcers in which the combination of neuropathy and peripheral arterial disease exists in the same individual, together with some form of trauma, are becoming increasingly common in diabetes foot clinics.

The main risk factors for peripheral arterial disease in diabetes are hyperlipidaemia, hypertension, history of cardiovascular disease, and cerebrovascular disease. A smoking history and being male are also significant influences [17]. Clinical manifestation of peripheral arterial disease is commonly through symptoms of intermittent claudication, but it can progress to tissue necrosis and gangrene in the latter stages (Figure 53.4) [17].

The term *chronic limb-threatening ischaemia* has been recommended by the Global Vascular Guidelines to encompass the broad spectrum of arterial disease presentations and the relative risk of amputation [18]. *Critical limb ischaemia* is reserved for the most severe form and defined as the presence of peripheral arterial disease in combination with rest pain, gangrene, or lower-limb ulceration >2 weeks' duration [19].

Bedside screening tools for peripheral arterial disease

Screening for vascular disease can be difficult in individuals with diabetes, as many are asymptomatic or report atypical symptoms. During the screening process it is important to establish whether there is any ischaemic rest pain at night, intermittent claudication, and history of vascular procedures such as bypass or angioplasty [19].

Palpation of the posterior tibial and dorsalis pedis pulses to determine their relative presence or absence can be influenced by practitioner skill and/or room temperature and should therefore be interpreted with caution. A Doppler ultrasound probe can assess flow signal waveforms, but vessel wall calcification can give a falsely elevated reading on an ankle brachial pressure index [19].

Individuals being considered for imaging modalities requiring the use of contrast must be identified as safe for contrast use in the context of renal disease [13].

Long-term risk factors for foot ulceration

Previous foot ulceration and/or amputation are the most important risk factors for developing a foot ulcer. In some series, the annual recurrence rate is up to 50% and, although there are a plethora of influencing factors, psychosocial and behavioural components are increasingly recognized. Studies of behaviour and attitudes of

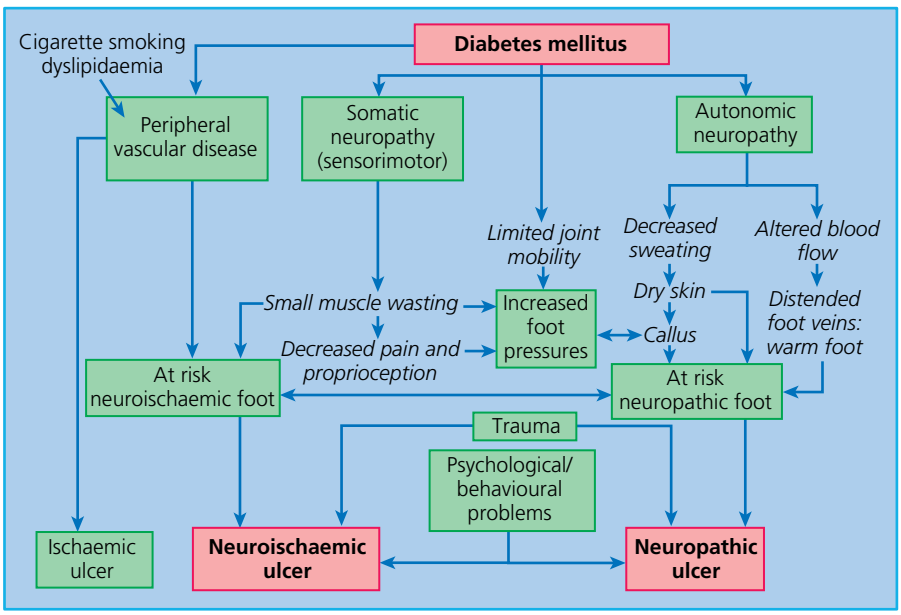

Figure 53.3 Pathways to foot ulceration in diabetes.

Figure 53.4 Infected diabetes-related foot lesion, necrotic 2nd digit, surrounding erythema and purelent discharge suggesting infection.

people with diabetes-related foot ulcerations have identified that individual perception of risk does not necessarily concur with clinician assessment and that behaviour is driven by the individual's own perception [20].

Renal disease, even at the preliminary stage of microalbuminuria, is a strong predictor of foot ulceration. Individuals most at risk include those with end-stage renal disease receiving dialysis or renal transplant/combined pancreas–renal transplants. The latter group are often described as being *non-diabetic* postoperatively and their newly increased energy levels are often accompanied by an increase in activity levels. However, the sensorimotor and autonomic peripheral nerves remain in their *diabetic* state; that is, neuropathic [13].

The risk of ulceration and amputation can increase two- to four-fold with age, and the relationship between duration and prevalence is equal for type 1 diabetes and type 2 diabetes. Men have a 1.6-fold increased risk of ulceration and amputation compared to women. Foot ulcers are more common in white Europeans than in people from other ethnic backgrounds [13].

Pathway to ulceration

Psychosocial factors together with abnormalities in pressures and loads under the foot are contributory factors to foot ulceration [21]. Peripheral and autonomic neuropathies represent the commonest long-term complications of diabetes and as such are the key components in the pathogenesis of diabetic foot ulceration [22].

Plantar callus

Callus accumulates under weight-bearing surfaces where skin is dry due to autonomic neuropathy. Exposure to repetitive stresses from focal high-pressure areas in the foot increases callus formation [22]. It acts as a foreign body and may cause ulceration.

Elevated foot pressures

A plethora of studies have confirmed the role of abnormal plantar pressures in the formation of diabetes-related foot ulcers. Studies have employed a variety of techniques, such as pedobarography and other expensive imaging modalities to obtain data, but in clinical practice they are not required (Figure 53.5) [23].

Foot deformities

Foot deformities contribute to ulceration through increased pressures and may include motor neuropathy, cheiroarthropathy, increased small muscle wasting (intrinsic minus), prominent metatarsal heads, and clawing of the toes, which are said to result in the high-risk neuropathic foot (Figure 53.2) [13].

Prevention of diabetes-related foot ulcers

Research of diabetes-related foot ulceration has primarily focused on interventions to promote healing [24] and this is mirrored in clinical practice. Prevention of foot ulceration is poorly studied and within health systems underfunded. A paradigm shift from stratified healthcare towards personalized medicine for diabetes-related foot disease is required [24]. Focusing on prevention of foot ulceration should be at the forefront of foot care to achieve better outcomes for individuals with diabetes and reduce the immense burden on global healthcare systems. Modifiable risk factors should focus on all aspects of evidence-based offloading devices, barefoot and in-shoe pressure factors, as well as tissue stress patterns [25]. Such strategies can be delivered in an integrated, objective, quantitative, and evidence-based approach [25].

The International Working Group on the Diabetic Foot has identified five important elements in the prevention of foot ulcers:

- Identifying the at-risk foot.
- Regularly inspecting and examining the at-risk foot.
- Educating the person with diabetes, their family, and healthcare professionals.
- Ensuring routine wearing of appropriate footwear.
- Treating risk factors for ulceration [25].

Foot care education is crucial in the prevention of ulceration, although there is little evidence available to support this in terms of randomized controlled trials [25]. Nevertheless, clinicians have a responsibility to comprehensively evaluate and educate individuals with diabetes, empowering them to engage in self-care and active

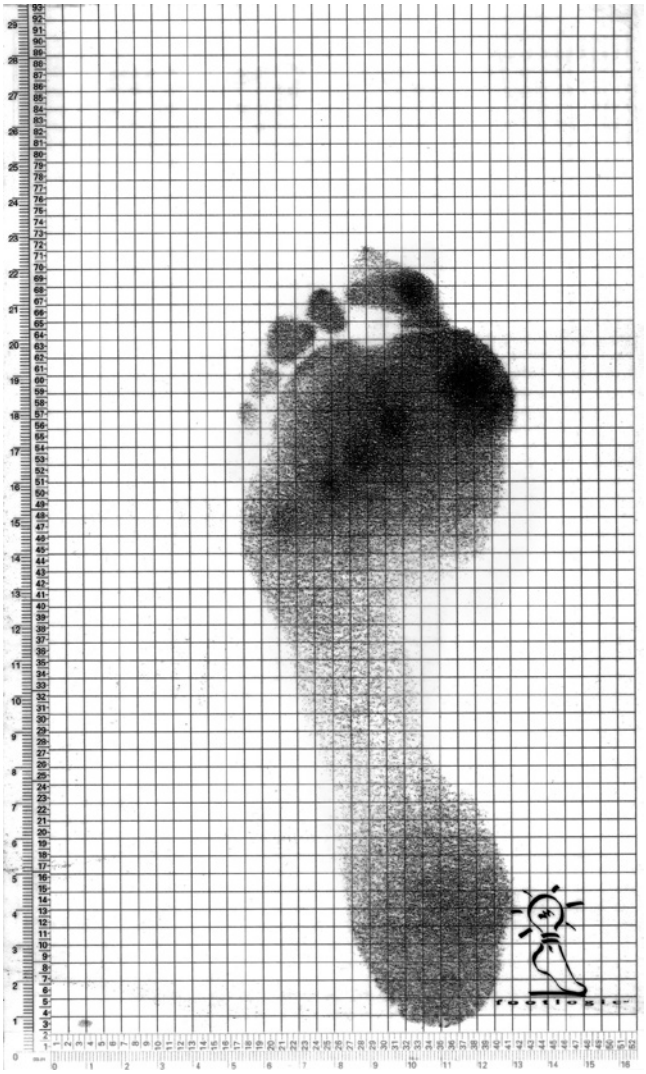

Figure 53.5 A black-and-white pressure distribution of one footstep using PressureStat: the darkest areas represent highest pressures, in this case under metatarsal heads 1 and 3 and the hallux.

prevention of foot ulceration [14]. A structured diabetes education programme is an essential component of preventive care [14]. Engagement with family members and carers may also be necessary to improve and reinforce self-care in people with foot ulcers [26].

Footwear

Appropriate footwear is vital in the reduction of foot ulcer occurrence and recurrence (Figure 53.6) [25]. Randomized controlled trials support the use of specialist hosiery with the potential to reduce foot pressures and provide protection for the high-risk neuropathic foot [25]. Mobilizing the bare foot is an absolute contraindication even while standing or sitting and should be reinforced at all times [25].

Skin temperature

Monitoring of skin temperature combined with preventive action when a temperature threshold is breached has been reported as effective in preventing diabetes-related foot ulcers [27]. However, the reliability of home thermometers in detecting temperature changes is questionable. It is also difficult to determine whether the positive effect originated with the temperature or visualization of the foot while obtaining the temperature [27].

Figure 53.6 Inappropriate footwear high heel wedge increasing forefoot plantar pressures.

Foot ulcer classification

SINBAD (Site, Ischaemia, Neuropathy, Bacterial infection, And Depth) is the most commonly used evidence-based international classification system for diabetes-related foot ulceration and is advocated by the International Working Group on the Diabetic Foot [28]. SINBAD is recognized by health professionals as a *common language* used in communicating information about diabetes-related foot ulcers [28].

In 2014 the Society for Vascular Surgery published the Wound Ischaemia and Infection (WIfI) classification system for the clinical staging of chronic limb-threatening ischaemia, to review amputation risk and need for revascularization (Figure 53.7) [29]. The WIfI classification is especially useful in predicting the possibility of amputation for one year and has benefits to assist with the management of individuals who have presented with a foot ulcer [30].

Wound healing in the diabetic foot

The management and healing of diabetes-related foot ulcer are a global challenge [13]. Adverse outcomes are common, including delay and failure to heal, infection, sepsis, amputation, and the high risk of recurrence [13]. Biological elements such as loss of protective sensation, abnormal biomechanics, peripheral arterial disease, and persistent infection create a difficult environment for a diabetes-related foot ulcer to heal successfully [13].

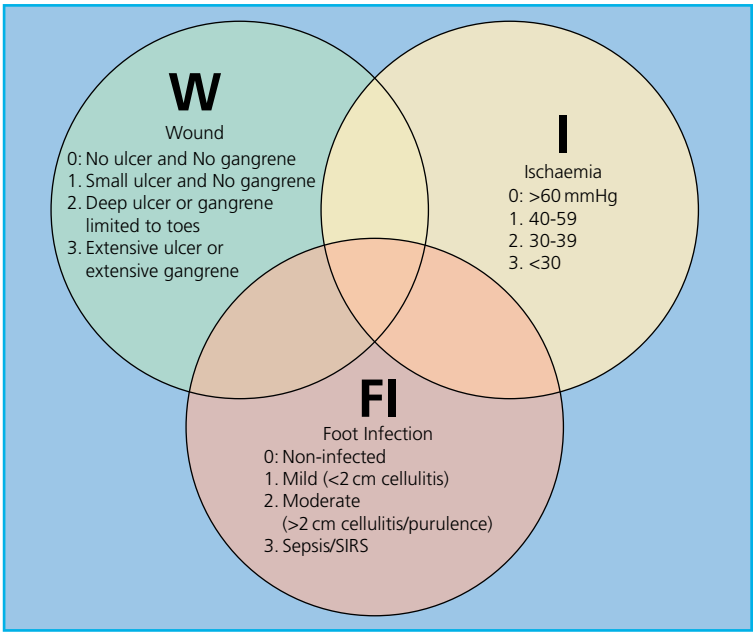

Figure 53.7 The Wound Ischaemia and Infection (WIfI) classification system for the clinical staging of chronic limb threatening ischaemia. The three circles represent Wound, Ischaemia and Foot Infection.

Impaired wound healing occurs due to low cellular proliferation rates, irregular keratinocyte differentiation, and slow angiogenesis [31]. People with end-stage renal disease and moderate to severe comorbidities relating to diabetes are at higher risk of non-healing ulcers and lower-limb amputation [32].

A vital component of wound management is removal of slough, necrotic tissue, and surrounding callus utilizing sharp debridement, subject to contraindications such as increased pain or severe ischaemia [33]. Products available for wound protection can be divided into broad categories of those with debriding properties, antiseptic-based dressings, those that are moisture providing, and those that influence the healing process [33].

Offloading

Decades of extensive evidence have cemented offloading as a highly effective intervention for healing diabetes-related foot ulcers. A total contact cast was considered the gold standard treatment for plantar foot ulcers; however, prefabricated, removable, knee-high walkers can be modified to non-removable and are as effective as the total contact cast [34]. There are several different offloading devices that are defined as an *ankle-high offloading device*, such as an ankle-high walker, forefoot offloading shoe, cast shoe, healing sandal, postoperative healing shoe, and custom-made temporary shoe [34]. Further research is required for the use of ankle-high offloading due to the alteration in mechanical stress [34]. Mechanical stress levels leading to different healing outcomes, such as plantar pressure, shear stress, and weight-bearing activity, need to be a focus for future research and randomized controlled trials. There are limited data relating to offloading in the healing of plantar ulcers in complicated infection or ischaemia, heel ulcers, and non-plantar ulcers [34].

Although effective offloading is vital in the successful healing of diabetes-related foot ulcer, total contact casting is contraindicated for ischaemic ulcers and osteomyelitis due to the risk of additional complications associated with poor arterial inflow. Total contact casts by their nature prevent wound monitoring, thereby preventing the early detection of iatrogenic pressure wounds [34]. The removal of pressure, eradication of infection, appropriate wound management, and restoration of perfusion are key factors necessary for successful wound closure [13].

Dressings

Dressings are used to keep the surface of diabetes-related foot ulcers protected from trauma and infection and to ensure the wound surface has the correct level of moisture required for the stage of healing [35]. Appropriate dressings enhance healing of diabetes-related foot ulcers. There is a wide variety of dressings available, necessitating careful consideration of the wound's current stage in the healing process and its specific characteristics prior to selection [35] (Table 53.1).

Management of infection

Appropriate wound debridement and offloading together with antibiotics are vital in the management of infected foot ulcers. There is no evidence to suggest that clinically non-infected neuropathic ulcers warrant treatment with oral antibiotics; however, some evidence suggests a benefit from antibiotics in treating neuroischaemic ulcers. Caution and clinical vigilance should prevail when treating infected diabetes-related foot ulcers with antibiotics [36]. A recent large-scale randomized clinical trial, the Oral Vs IntraVenous Antibiotics study (OVIVA), demonstrated that people randomized to oral versus intravenous antibiotics showed no superiority with either delivery modality [36].

The severity of infection of diabetes-related foot ulcers is related to location, depth (fascia, muscles, tendons, joints or bone), presence of necrosis, and/or gangrene [13]. If foot infections are not managed promptly, serious complications can result in lower-extremity amputations [13]. On presentation 60% of diabetes-related foot ulcers are already infected [13]. Pathogens such as Gram-positive *Staphylococcus aureus*, pseudomonas, and *Enterobacteriaceae* species easily enter the wound and to a lesser extent streptococcus Gram-negative species can thrive [13]. Anaerobic infection must also be considered in neuroischaemic ulcers [13].

Delayed healing can occur due to the complex microbiome and polymicrobial organization on the surface of the wound.

Table 53.1 Dressings that can be used to treat diabetes-related foot ulcers.

Dressing	Description	Contraindications
Hydrocolloid	Facilitates rehydration and autolytic debridement Dry, sloughy, necrotic wounds Promotes granulation.	Infected wounds Twice-weekly change
Hydrogels	Donates liquid to dry wounds and absorbs exudates Dry, sloughy wounds Autolytic debridement	Hydrogel sheets avoided in infected wounds
Silver	Antimicrobial Colonization	Sensitivity to silver
Vapour-permeable	Provides a moist healing environment Mild exudates	Heavily exudating wound
Foam dressing	Primary or secondary cover Light and heavy exudates	Remove if strike-through occurs
Odour-absorbent	Absorbs odour Malodorous	Silver (sensitivity)
Larval therapy	Debridement, promotes granulation Heavily sloughy necrotic wounds	Increase in pain
Alginate	Haemostat Heavy exudates	Blockage Loose fibres
Skin substitutes	Living skin Obstinate wounds	Colonized Infected wound
Iodine	Antibacterial Exudating wounds	Iodine (sensitivity) Renal/thyroid conditions
Honey	Antimicrobial Sloughy necrotic wounds Autolytic debridement	Medical grade only

Multidrug-resistant Gram-negative strains of bacteria such as highly resistant pseudomonas, extended-spectrum β-lactamase, and carbapenemase-producing Gram-negative bacilli are commonly found in cultures of diabetes-related foot ulcers [37].

Inflammatory response to pathogens can be reduced or absent in individuals with neuropathy and ischaemia, with ~50% of presenting foot ulcers being asymptomatic for infection [13]. Pain, warmth, erythema, raised C-reactive protein, tenderness, prolonged healing, and wound malodour are indicators of infection. Poor granulation tissue and increased purulent discharge often occur with chronic hyperglycaemia [13].

To implement a specific and effective antibiotic regimen, tissue samples or deep wound swabs should be taken for culture and sensitivity, as superficial cultures are very often contaminated by colonizing bacteria [13]. It is most effective to swab foot ulcers following curettage and aggressive debridement if appropriate [13].

Empirical antibiotic therapy against *Staphylococcus aureus* and aerobic streptococci should be started until conclusive culture results are obtained. Antibiotic agents are appropriate against Gram-negative organisms for suspected severe infection. There is limited evidence for the use of topical antimicrobial treatments. For soft tissue infections, the following agents should be considered: penicillins, cephalosporins, carbapenems, metronidazole, clindamycin, linezolid, daptomycin, fluoroquinolones, or vancomycin, but not tigecycline [38].

Intravenous antibiotic administration is only indicated in severe infections (bacteraemia), as most mild to moderate infections will respond to oral antibiotics with a high bioavailability. Antibiotic treatment alone is insufficient for managing diabetes-related foot ulcers and additional interventions are also necessary, including sharp debridement, drainage of purulent discharge, and appropriate offloading [38].

Wounds with extensive bone and soft tissue involvement require deep and aggressive debridement to remove non-viable tissue and provide drainage of purulent discharge [38]. Complete surgical excision can significantly reduce the number of days taken to heal compared with ulcers managed more conservatively [38].

Osteomyelitis

Osteomyelitis frequently affects the forefoot, with over 90% of infections occurring at this site, 5% in the midfoot, and 5% in the hindfoot; however, osteomyelitis can occur in any bone. Forefoot osteomyelitis has a better prognosis than midfoot or hindfoot osteomyelitis [13]. Early and accurate diagnosis is vital to ensure treatment with a suitable antibiotic agent and reduce the risk of minor and major amputation [13].

A useful clinical sign suggesting osteomyelitis in a digit is a sausage-shaped swelling. The probe-to-bone test is a useful tool in the evaluation of osteomyelitis. The procedure involves inserting a blunt probe into the soft tissue deficit. A hard endpoint (solid or gritty) indicates a positive finding. The anatomical location and the performer's expertise may affect reliability. A positive probe-to-bone test finding in a high-risk individual indicates a high probability of osteomyelitis. A negative probe-to-bone test result in a low-risk person indicates a low probability of osteomyelitis [13].

The gold standard for the diagnosis of osteomyelitis is bone biopsy, which provides histological and microbiological findings [13]. A combination of the probe-to-bone test, C-reactive protein and/or procalcitonin levels, erythrocyte sedimentation rate (ESR), and plain X-rays should be carried out in suspected osteomyelitis (Figure 53.8) [34]. If a diagnosis cannot be reached, advanced imaging studies such as magnetic resonance imaging scan, 18F-fluorodeoxyglucose positron emission tomography/computed tomography (CT), or leucocyte scintigraphy (with or without CT) may be required [39]. Clinically relevant bone microorganisms should be sent to histopathology for culture and sensitivity as early as possible [13].

Antibiotic therapy should be based on the likely or proven causative pathogen(s) and their susceptibilities; the clinical severity of the infection; published evidence of efficacy of the agent for diabetic foot infections; risk of adverse events, including collateral damage to the commensal flora; likelihood of drug interactions; and agent availability [38]. Individuals with osteomyelitis have a higher rate of recurrence after initial treatment and a longer time to healing compared to soft tissue infections [38].

Surgical resection of the infected portion of bone once all conservative options have failed has been the mainstay for treating osteomyelitis, but increasing evidence from case series and a randomized controlled trial reports that osteomyelitis localized to one or two phalanges may be successfully treated with antibiotics alone. There is no evidence base to advise the optimal duration of antibiotic therapy for osteomyelitis, but a recent trial suggests that six weeks' antibiotic therapy may be sufficient [13]. Osteomyelitis in the diabetic foot is often due to long-standing non-healing ulcers and has an associated high risk of minor and major amputation [13].

Figure 53.8 This radiograph displays two main abnormalities: changes of osteomyelitis and septic arthritis involving the first metatarso-phalangeal joint, with destruction of the distal first metatarsal and proximal area of the proximal phalanx of the great toe; and chronic changes of Charcot neuroarthropathy in the first cuneiform/metatarsal area.

Negative pressure

Negative-pressure devices significantly reduce wound-closure times and improve the healing rates of foot ulcers with no increase in complications [40]. Increased perfusion and granulation tissue are the reported benefits from cell deformation [40]. A recent systematic review confirmed that there was some evidence to support the use of negative-pressure devices in surgical wounds [40].

Hyperbaric oxygen

Although hyperbaric oxygen therapy is not recommended specifically for treating diabetes foot wounds [41], initial trials of topical oxygen treatment have shown promise in treating diabetes-related foot ulcers and further studies are ongoing [42].

Surgical management

Surgical management is based on expert opinion and at best case series reports. Surgical interventions may be considered if conservative options have failed and may include Achilles' tendon lengthening, metatarsal head resection, internal/external fixation, and flexor–extensor tendon lengthening. Tissue fillers can also be used for loss of fatty pad; however, evidence is limited and surgical intervention poses increased risks [39]. Surgery should only be considered once all non-surgical options have been explored, as 75% of wounds will heal without any form of surgical intervention [39].

Charcot neuroarthropathy

Charcot neuroarthropathy is a devastating complication of diabetic neuropathy, which can result in extensive bone and joint destruction, increased risk of ulceration, infection, and amputation if not properly managed (Figure 53.9) [43]. Active Charcot neuroarthropathy characteristically presents with localized swelling, erythema, and increased temperature (>2 °C compared to the contralateral foot) to the affected foot. In individuals with peripheral neuropathy, pain may not always be present and is only reported in 50% of individuals with diabetes [43]. Therefore individuals presenting with the characteristic symptoms in the context of a history of peripheral neuropathy and/or renal failure should be considered to have Charcot neuroarthropathy until proven otherwise. Advanced presentations of Charcot neuroarthropathy may be characterized by a foot deformity, particularly a *rocker-bottom* deformity.

Management

Immobilization until complete resolution of the active phase is required. Total contact casting or removable walkers are suitable; however, if total contact cast is used, it must be replaced every 1–2 weeks to adjust for limb volume changes from oedema reduction and to assess for any complications secondary to immobilization [34]. Bilateral Charcot neuroarthropathy is reported in 30% of cases [34]; it is thought that immobilization of one foot may increase the load on the contralateral foot, predisposing to bilateral active Charcot neuroarthropathy. Therefore prophylactic support with appropriate footwear and insoles is recommended for the contralateral foot to minimize the risk of bilateral active Charcot neuroarthropathy [34].

Periodic follow-up radiographs are required to monitor the progression of Charcot neuroarthropathy and changes in the architectural alignment of the foot [34]. Three-monthly reviews are required for such high-risk individuals to monitor the development of recurrent or new episodes, along with other foot complications [43]. If the correct diagnosis is made in the active phase of Charcot neuroarthropathy and conservative treatment is successful, surgery may be avoided [43] and the risk of ulceration and amputation reduced. Surgical management is considered in the inactive phase of Charcot neuroarthropathy where joint instability has failed. Surgical intervention is generally avoided during the active phase of Charcot neuroarthropathy due to a high risk of secondary infection [43].

Figure 53.9 X-ray of chronic Charcot foot demonstrating neuroarthopathic changes in the midfoot with peri-talar destruction.

Conclusion

Peripheral neuropathy plays a central role in the development of foot lesions through the loss of protective sensation, as the absence of pain renders the foot highly vulnerable to trauma without awareness. The International Working Group on the Diabetic Foot reported on the details required in the planning and reporting of intervention studies in the prevention and management of foot diabetic disease. Guidelines for the prevention and treatment of diabetes-related foot disease are invaluable in creating the standards of care necessary to achieve a reduction in amputations.

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54 Sexual Function in Men and Women with Diabetes

Kirsty Winkley[1], Camilla Kristensen[1], Jackie Fosbury[2], and David Price[3]

[1] King's College London, London, UK
[2] Sussex Community NHS Foundation Trust, Brighton, UK
[3] Morriston Hospital, Swansea, UK

Key points

- The prevalence of erectile dysfunction in men with diabetes increases with age and is about 35–50% overall.
- Penile erection occurs as a result of engorgement of the erectile tissue following vascular smooth muscle relaxation in the corpus cavernosum mediated by nitric oxide (NO), which is derived from both parasympathetic nerve terminals and the vascular endothelium.
- Erectile dysfunction in diabetes is largely due to failure of NO-mediated smooth-muscle relaxation secondary to endothelial dysfunction and autonomic neuropathy.
- Erectile dysfunction is an early indicator of endothelial dysfunction and a marker of increased cardiovascular risk.
- Sildenafil and other phosphodiesterase 5 (PDE5) inhibitors act by inhibiting the breakdown of cyclic guanosine monophosphate, the second messenger in the NO pathway, and hence enhance erections under conditions of sexual stimulation.
- PDE5 inhibitors are safe and effective and can be used to treat erectile dysfunction in a diabetes clinic or general practice.
- Other options for treating erectile dysfunction in diabetes are intracavernosal injection therapy, transurethral alprostadil, vacuum therapy, and surgical insertion of penile prostheses.
- In women with diabetes, sexual dysfunction is twice as common than in women without diabetes and women may not be aware diabetes is a cause.
- Sexual dysfunction is associated with high and low blood glucose levels, depression, and body image issues in women with diabetes.
- There are no licensed pharmacological treatments for women with diabetes and sexual dysfunction, although PDE5 inhibitors may have some benefit. There have been no published studies on psychological interventions for women with diabetes and sexual dysfunction.
- Contraceptive advice is essential in diabetes, as unplanned pregnancies carry an increased risk of morbidity and fetal abnormalities. Most forms of contraception are safe and effective in women with diabetes, but the oral contraceptive pill is recommended, as it is reliable and well tolerated.
- Hormone replacement therapy should be considered on a short-term basis in all women with an appropriate indication, particularly if they have diabetes. It has no adverse effects on glycaemic levels or lipid profiles.

Male erectile dysfunction

Erectile dysfunction is one of the commonest clinically apparent complications in men with diabetes. It can cause distress, but is usually treatable. It may also be a marker of cardiovascular risk, and so it is a condition that all diabetes professionals should be aware of and understand.

Physiology of erectile function

Tumescence is a vascular process under the control of the autonomic nervous system. The erectile tissue of the corpus cavernosum behaves as a sponge, and erection occurs when it becomes engorged with blood. Dilatation of the arterioles and vasculature of the corpus cavernosum leads to compression of the outflow venules against the rigid tunica albuginea (Figure 54.1) [1, 2]. Hence smooth-muscle relaxation is the key phenomenon in this process, as it leads to increased arterial inflow and reduced venous outflow [3, 4]. The process is under the control of parasympathetic fibres, which were previously known as non-adrenergic, non-cholinergic neurones, as the neurotransmitter was unknown; however, it is now clear that nitric oxide (NO) is the agent largely responsible for smooth-muscle relaxation in the corpus cavernosum. It is both produced in the parasympathetic nerve terminals and generated by NO synthase in the vascular endothelium. Within the smooth-muscle cell of the corpus cavernosum, NO stimulates guanylate cyclase, leading to increased production of the second messenger, cyclic guanosine monophosphate (cGMP), which induces the activation of protein kinase G. This inhibits calcium release, which leads to smooth-muscle relaxation (Figure 54.2) [5, 6]. Neuronally derived NO is important in initiation, whereas NO from the endothelium is responsible for maintenance of erection [7].

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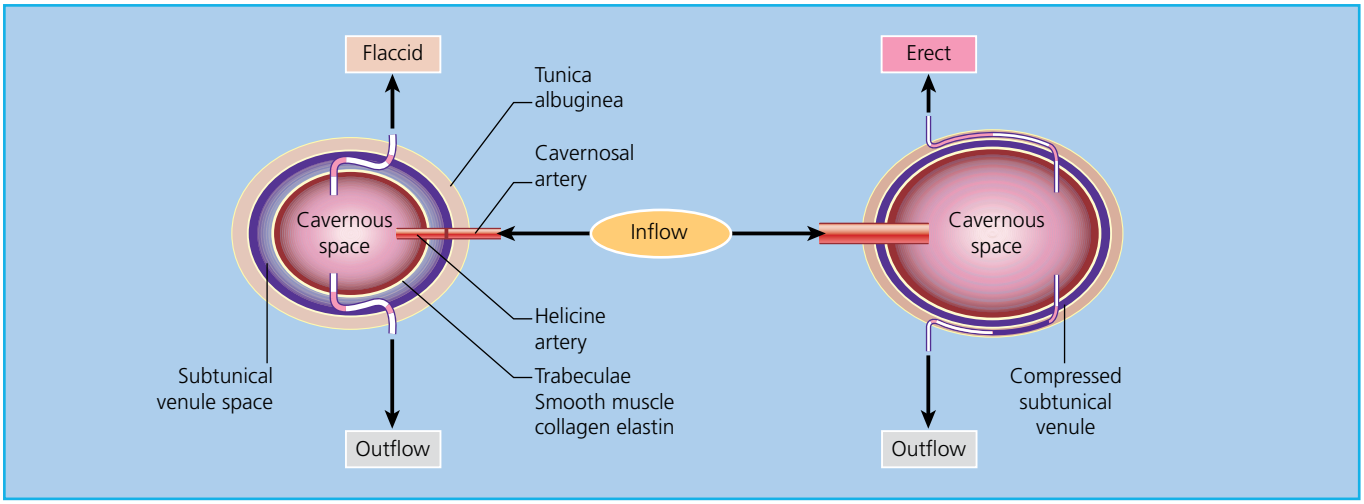

Figure 54.1 Diagrammatic representation of the corpus cavernosum. During tumescence, dilatation of the helicine and cavernosal arteries produces expansion of the cavernosal space and compression of the outflow venules against the rigid tunica albuginea.

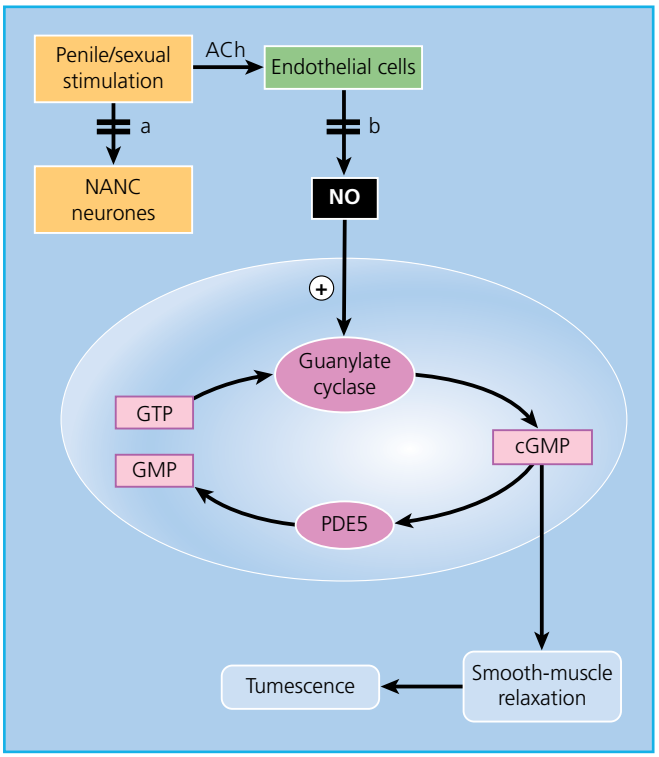

Figure 54.2 Pathophysiology of erectile function in diabetes. Diagrammatic representation of the pathways leading to the relaxation of a corpus cavernosal smooth-muscle cell. In diabetes there are defects in nitric oxide–mediated smooth-muscle relaxation due to neuropathy of (a) the NANC fibres and (b) endothelial dysfunction. ACh, acetylcholine; cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate; GMP, guanosine monophosphate; NANC, non-adrenergic, non-cholinergic neurones; NO, nitric oxide; PDE5, phosphodiesterase type 5.

Pathophysiology of erectile dysfunction in diabetes

In men with diabetes, erectile dysfunction is due to failure of NO-induced smooth-muscle relaxation from both autonomic neuropathy and endothelial dysfunction [8]. Many men with diabetes report that in the early stages they do not have a problem achieving an erection but that they cannot maintain it. This suggests that in these individuals failure of endothelium-derived NO occurs before significant autonomic neuropathy.

Other potential abnormalities may contribute to the development of erectile dysfunction in diabetes: endothelium-derived hyperpolarizing factor (EDHF) plays a role in endothelium-dependent relaxation of human penile arteries [9] and EDHF-mediated endothelium-dependent relaxation is significantly impaired in penile resistance arteries in men with diabetes [9]. Impaired EDHF responses might therefore contribute to the endothelial dysfunction of diabetic erectile tissue.

Increased oxygen free-radical levels in diabetes may reduce the vasodilator effect of NO. In particular, the formation of products of non-enzymatic glycation to produce advanced glycation end-products (AGEs) generates reactive oxygen species, which impairs NO bioactivity [10,11]. AGEs play a role in the development of microvascular and macrovascular disease in diabetes [12]. In animal models, inhibition of AGE formation improves endothelium-dependent relaxation and restores erectile function in diabetic rats [13,14].

Other pathophysiological changes known to occur in diabetes may contribute to erectile dysfunction, including non-enzymatic glycation of proteins, which impairs endothelium-dependent relaxation of the aorta in rats [15,16]. Other factors, not limited to diabetes, may also contribute to the development of erectile dysfunction in men with diabetes. Structural changes associated with large-vessel disease are commonly associated with erectile dysfunction in diabetes. However, this is usually associated with functional changes of widespread endothelial dysfunction in diabetes, and it is difficult to separate the relative importance of the two factors.

Testosterone has a central role in the physiology of erectile function and in the regulation of male sexual behaviour and attitudes. Hypogonadism is a well-established, and treatable, cause of erectile dysfunction. In experimental studies, androgen deficiency leads to a reduction in smooth-muscle and structural abnormalities in the erectile tissue [17,18]. In recent years, there has been interest in a potential association between reduced levels of testosterone and type 2 diabetes and the metabolic syndrome. However, it is controversial whether there is a causal link between diabetes and hypogonadism, and this will be discussed later in this chapter.

Other factors contributing to erectile dysfunction in diabetes

In addition to endothelial dysfunction and autonomic neuropathy, erectile dysfunction is associated with other conditions common in diabetes, such as hypertension and large-vessel disease [19]. A cross-sectional study of 550 Chinese men reported that in the 318 men with diabetes and erectile dysfunction the prevalence of diabetes complications – that is, cardiovascular disease, neuropathy, and nephropathy – was 1.7 times greater than for men with diabetes and no erectile dysfunction [20]. Furthermore, men with diabetes are more likely to be taking medications that can impair erectile function (Box 54.1). Antihypertensive agents are commonly reported to be associated with erectile dysfunction, although much of the evidence is anecdotal; β-blockers, aldosterone receptor blockers, and thiazide diuretics are the most commonly reported culprits [21]; the α-blockers perhaps have the least risk [22]. Finally, it should be remembered that there are many other potential causes of erectile dysfunction unrelated to diabetes, from which men with diabetes are not immune (Box 54.2).

Box 54.1 Medications associated with erectile dysfunction

Antihypertensives
Thiazide diuretics
β-blockers
Calcium channel blockers
Angiotensin-converting enzyme (ACE) inhibitors
Central sympatholytics (methyldopa, clonidine)
Aldosterone receptor antagonists

Antidepressants
Tricyclics
Monoamine oxidase inhibitors
(NB: Selective serotonin reuptake inhibitors can cause ejaculatory problems)

Antipsychotics
Phenothiazines
Haloperidol

Hormones
Luteinizing hormone-releasing hormone (goserilin, buserilin)
Oestrogens (stilbestrol)
Antiandrogens (cyproterone)

Miscellaneous
5α-Reductase inhibitors (finasteride)
Statins (simvastatin, atorvastatin, pravastatin)
Cimetidine
Digoxin
Metoclopramide

Drugs of abuse
Alcohol
Tobacco
Marijuana
Amphetamines
Anabolic steroids
Barbiturates
Opiates

Box 54.2 Conditions associated with erectile dysfunction

Psychological disorders
Anxiety about sexual performance
Psychological trauma or abuse
Misconceptions
Sexual problems in the partner
Depression
Psychoses

Vascular disorders
Peripheral vascular disease

Hypertension
Venous leak
Pelvic trauma

Neurological disorders
Stroke
Multiple sclerosis
Spinal and pelvic trauma
Peripheral neuropathies

Endocrine and metabolic disorders
Diabetes
Hypogonadism
Hyperprolactinaemia
Hypopituitarism
Thyroid dysfunction
Hyperlipidaemia
Renal disease
Liver disease

Miscellaneous
Surgery and trauma
Smoking
Drug and alcohol abuse
Structural abnormalities of the penis

Clinical aspects of erectile dysfunction in diabetes

Erectile dysfunction becomes more prevalent with age. In a population-based study in Massachusetts, USA, the prevalence of complete erectile failure was reported to be 5% in men in their 40s and 15% in those over 70 years of age [19]. In younger sexually active men aged 18–31 years (n = 2660) in the Growing Up Today study, mild erectile dysfunction was present in 11.3% and moderate to severe in 2.9% [23]. By contrast, a systematic review and meta-analysis of 145 studies including 88 577 men with diabetes demonstrated a much higher prevalence of 52.5% overall (95% confidence interval [CI] 48.8 to 56.2), 37.5% for men with type 1 diabetes, and 66.3% for men with type 2 diabetes [24]. The prevalence in men with diabetes also increases with age. In a survey of men attending a hospital diabetes clinic in the UK, the prevalence of erectile dysfunction increased from 13% among 30-year-olds to 61% among men aged over 60 years [25] (Figure 54.3). Overall the prevalence was 38%. The prevalence of erectile dysfunction in diabetes in a general practice population was even higher, at 55% [19]. These data suggest that erectile dysfunction is the commonest clinically apparent complication of diabetes in men.

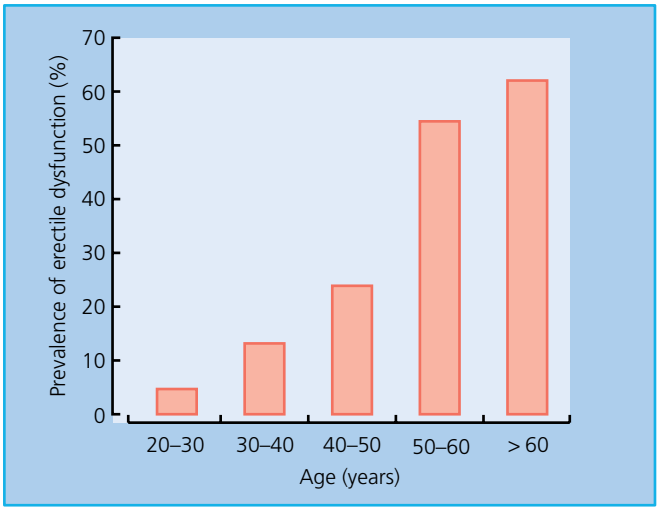

Figure 54.3 Prevalence of erectile dysfunction by age of men attending a hospital diabetes clinic. Source: Data from Price et al. 1991 [25].

Conversely, diabetes is a common finding in men presenting with erectile dysfunction. Approximately 20% of men seen in erectile dysfunction clinics have diabetes, of whom ~5% were previously diagnosed [26, 27].

The presence of other medical conditions increases the risk of erectile dysfunction. A population-based survey of 600 men in Brazil, Italy, Japan, and Malaysia examined the prevalence of erectile dysfunction and its relationship to other diseases and lifestyles. The prevalence of erectile dysfunction among men with diabetes rose from 25% at age 40–44 to 70% at age 65–70 years [28]. Cardiovascular disease increased the risk of erectile dysfunction. The prevalence was 31.7% in men with diabetes only, 40% in men with diabetes and heart disease, and 46.5% in those with diabetes and hypertension. Men with diabetes who smoked and reported below-average levels of physical activity had a fourfold increase in the prevalence of erectile dysfunction.

Erectile dysfunction as a risk factor for cardiovascular disease

There is convincing evidence of an association between erectile dysfunction and both cardiovascular disease [29, 30] and mortality [31]. This may be because they share common risk factors. Increased waist measurement and reduced physical activity, both important risk factors for ischaemic heart disease, considerably increase the risk of erectile dysfunction [32–34].

The association between erectile dysfunction and cardiovascular disease may be due to more than shared risk factors and may arise because they are both manifestations of endothelial dysfunction, which has a key role in the pathogenesis and progression of atherosclerosis [35]. It is clear that the endothelium has important and complex endocrine and paracrine functions, and one of its most important products is NO (previously known as endothelium-derived relaxing factor). NO derived from both nerve terminals and the vascular endothelium has a central role in the physiology of erection. Therefore, there are theoretical grounds to believe that erectile dysfunction might be an early marker of endothelial dysfunction and hence an important risk factor for cardiovascular disease, and there is evidence to support this case in animal studies [36] and humans [37, 38].

Hence the association between erectile dysfunction and increased cardiovascular risk may be a case of shared *common soil*, in particular endothelial dysfunction and microvascular disease. In practical terms, this means that cardiovascular risk should be assessed in any man with erectile dysfunction whether he has diabetes or not. A man with type 2 diabetes and erectile dysfunction has approximately double the risk of developing coronary heart disease compared with a similar man without erectile dysfunction [29].

Smoking and alcohol consumption

Smoking greatly increases the risk of developing erectile dysfunction. A follow-up of the Massachusetts Male Aging Study reported that cigarette smoking almost doubled the risk of developing erectile dysfunction after about seven years [19]. A similar finding was reported by the large Health Professionals' Follow-up Study [32]. Smoking appears to exert its effects via the NO signal transduction pathway [39].

In contrast to tobacco, it is well-established that moderate alcohol consumption is associated with a reduced risk of a cardiovascular event. It is interesting that drinking alcohol in moderation also appears to reduce the risk of developing erectile dysfunction [40], whereas men with alcohol dependence are more likely to experience it [41].

Quality-of-life issues

That erectile dysfunction can significantly worsen a man's quality of life is beyond doubt and treating erectile dysfunction improves quality of life. A large study of men with type 2 diabetes reported that erectile problems were associated with a dramatic increase in depressive symptoms [42]. In another series in general practice, 45% of men with diabetes stated that they thought about their erectile dysfunction all or most of the time, 23% felt that it severely affected their quality of life, and 10% felt that it severely affected their relationship with their partner [43]. More recently, a study of 100 men with diabetes, of whom 90% had type 1 diabetes, demonstrated that 66% had erectile dysfunction and almost 50% of them had not sought help [44]. The same study also reported high rates of depressive symptoms, anxiety, and relationship difficulties in those experiencing sexual issues [44]. A systematic review of randomized trials of erectile dysfunction treatment reported improvements in self-esteem, confidence, and depression scores after treatment [45].

Assessment and investigation of erectile dysfunction in diabetes

Clinical assessment

If health professionals do not start the conversation to ask about erectile dysfunction and the man raises the subject, it is likely he is anxious about the problem. However, once the subject has been broached, men with erectile dysfunction and their partners (if present) do not usually have any difficulty discussing the problem. A description of the nature of the erectile dysfunction should be obtained, to ensure that the man is experiencing erectile dysfunction and not another related problem, such as premature ejaculation (Box 54.3). General physical examination may give clues as to the aetiology of erectile dysfunction and the choice of treatment (Box 54.4). The suggested investigations of erectile dysfunction in diabetes are listed in Box 54.5. These cover psychological issues, hypogonadism, cardiovascular issues, and urological problems. Comorbid depression is common in people with diabetes [46] and

Box 54.3 Key features in the history of erectile dysfunction in diabetes

Onset usually gradual and progressive
Earliest feature often inability to sustain erection long enough for satisfactory intercourse
Erectile failure may be intermittent initially
Sudden onset often stated to indicate a psychogenic cause, but little evidence to support this
Preservation of spontaneous and early-morning erections does not necessarily indicate a psychogenic cause
Loss of libido consistent with hypogonadism but not a reliable symptom
Men with erectile dysfunction often understate their sex drive for a variety of reasons

Box 54.4 Key physical signs on examination

Any features of hypogonadism
Manual dexterity – may preclude physical treatment
Protuberant abdomen
External genitalia:
Presence of phimosis
Testicular volume
Peyronie's disease
Balanitis

Box 54.5 Investigation of erectile dysfunction in diabetes

Serum testosterone if libido reduced or hypogonadism suspected (ideally taken at 9 a.m.)
Serum prolactin and luteinizing hormone if serum testosterone subnormal
Assessment of cardiovascular status if clinically indicated:
ECG
Serum lipids
Glycated haemoglobin, electrolytes, if clinically indicated
Psychological screening:
Depression
Anxiety
Urological assessment if clinically indicated

depression is associated with onset of erectile dysfunction in men with diabetes [47]; poor self-esteem and anxiety may follow these comorbid problems, exacerbating the problem of erectile dysfunction [48]. Few investigations are needed, but it is worth excluding other treatable causes of erectile dysfunction; in practical terms, hypogonadism is the only treatable one. The relationship between diabetes and hypogonadism is a matter of debate (see later), but gonadal function should be assessed in all men with diabetes and erectile dysfunction. Some men presenting with erectile dysfunction will not have attended any form of clinic for many years, and so the consultation provides an opportunity to address other health issues. For the reasons outlined earlier, consideration should be given to assessing the man's cardiovascular status. The consultation also provides an opportunity to address the management of the man's diabetes.

General advice

As erectile dysfunction increases with age, most men with diabetes and their partners seeking treatment for erectile dysfunction are middle-aged. Diabetes healthcare professionals can offer an effective service for the treatment of erectile dysfunction in the absence of psychosexual counsellors [49–52]. It is important that the cause of the erectile dysfunction is explained, as many men will blame themselves. They should be advised that if they wish to resume sexual relations they will require long-term treatment, as spontaneous return of erectile function in diabetes occurs only rarely [53].

Treating erectile dysfunction in an attempt to save a failing relationship is rarely successful and may make the situation worse. The assistance of a suitably qualified psychosexual counsellor should be considered in this situation. Referral to a counsellor should also be considered if there is evidence of depression, anxiety, loss of attraction between partners, or marked performance anxiety. Any other medical problems should be addressed. Improving metabolic management may help general well-being, but suboptimal glycaemic levels should not be used as a reason to refuse or delay treatment. Men who smoke should be advised to stop for reasons of general health, although there is no good evidence that stopping smoking will improve erectile function in a man with diabetes.

Many men with diabetes will be taking medication known to cause erectile dysfunction. However, changing the treatment in an attempt to improve sexual function rarely works and may cause delays and frustration for the man. It is therefore not advisable unless there is a strong temporal relationship between starting treatment and the onset of erectile dysfunction.

Treatment options

The advent of effective oral therapies has transformed the management of erectile dysfunction. These should be offered as first-line therapy to men with diabetes, and the other treatment options should be reserved for those in whom oral therapy is contraindicated or ineffective.

Oral agents

Phosphodiesterase 5 inhibitors

Phosphodiesterase type 5 (PDE5) is an enzyme found in smooth muscle, platelets, and the corpus cavernosum. During tumescence, there is an increase in the intracellular concentration of NO, which produces smooth-muscle relaxation via the second messenger cGMP. This is broken down in turn by PDE5. Hence PDE5 inhibitors can enhance erections under conditions of sexual stimulation.

Sildenafil was the first PDE5 inhibitor and is a highly effective treatment for erectile dysfunction in men with and without diabetes [54, 55]. The first large study of 532 men with erectile dysfunction of mixed aetiology was published in 1998. In the group given sildenafil, 69% of all attempts at intercourse were successful, compared with 22% in those given placebo [56]. Other studies in men with erectile dysfunction of mixed aetiology have shown success

rates between 65% and 77% [56,57]. Studies of sildenafil have reported success rates of ~70% in hypertension [58], 76% in spinal cord injury [59], 63% in spina bifida [60], and 40% following radical prostatectomy [61].

In men with diabetes, the success rates for sildenafil are between 56% and 59% [58,62]. A study in older men reported success rates of 69% overall and 50% in men with diabetes [63]. Most of these studies of sildenafil have been short term, but a trial examining the long-term efficacy of sildenafil in men with erectile dysfunction due to a variety of causes reported that only 52% continued to use it after two years [64]. This figure may seem surprisingly low, but it is certainly considerably higher than for any other type of erectile dysfunction treatment.

Other phosphodiesterase type 5 inhibitors

There are currently four PDE5 inhibitors licensed for treatment: sildenafil, tadalafil, vardenafil, and avanafil, with two new additional agents, mirodenafil and udenafil, that are not yet widely available. Their key characteristics are listed in Table 54.1 and adverse effects from the key trials of PDE5 inhibitors in men with diabetes are given in Table 54.2 [65–70].

All four PDE5 inhibitors have similar efficacy and safety profiles. Their side-effect profiles differ slightly, but the most notable difference is the longer half-life of tadalafil. Thus a single dose of tadalafil offers the potential to restore erectile function to normal for two days and thereby remove the need for medication to be taken each time prior to sexual activity. The choice between this form of treatment and on-demand dosing is largely a matter of individual choice. Patient preference studies of agents with differing dosing instructions are difficult to perform in a blinded fashion, but these have generally shown a preference for tadalafil over sildenafil [71–75].

Adverse effects

Adverse effects related to PDE5 inhibitors are headache, dyspepsia, and flushing. Headache and flushing might be expected, as the inhibitors are vasodilators. Dyspepsia is usually mild and may be due to relaxation of the cardiac sphincter of the stomach. Abnormal vision is experienced by ~6% of men taking sildenafil; this may be because the drug has some activity against PDE6, which is a retinal enzyme. Back pain and muscle cramps are particularly an adverse effect of tadalafil. In all studies, the discontinuation rate due to adverse effects was low.

Cardiovascular safety of phosphodiesterase type 5 inhibitors

The launch of sildenafil, the first PDE5 inhibitor, was soon followed by case reports of cardiovascular events and deaths associated with its use. However, PDE5 inhibitors are not associated with increased cardiovascular risk [76–79]. Restoring sexual function is not completely without risk, as sexual activity, like any form of physical activity, can precipitate cardiovascular events in those at risk. A large case–control study reported that the risk of a cardiovascular event in the two hours after intercourse was increased 2.5-fold in healthy men and 3-fold if there was a history of previous myocardial infarction [80]. Although the absolute risk remains small, the issue of cardiovascular safety must be addressed in all men before treating erectile dysfunction. Jackson et al. suggested a classification scheme for assessing cardiovascular risk in men undergoing treatment for erectile dysfunction; those with the highest risk should be referred for specialist cardiac evaluation, whereas the lowest-risk group could be managed in primary care [79].

Drug interactions with phosphodiesterase type 5 inhibitors

PDE5 inhibitors can be used safely in men taking a wide range of drugs, but there are several potential important interactions. They are contraindicated in the presence of any nitrate therapy (including

Table 54.1 Characteristics of available phosphodiesterase type 5 inhibitors.

Agent	Dosage (mg)	Onset of action (min)	Half-life (h)	Duration (h)
Sildenafil	25, 50, or 100 PRN	30–60	3–5	<12
Vardenafil	5, 10, or 20 PRN	30–60	4–5	<10
Tadalafil	10 or 20 PRN or 5 daily	60–120	17.5	<36
Avanafil	50, 100, or 200 PRN		3	<6

PRN, as needed.

Table 54.2 Adverse effects of phosphodiesterase type 5 inhibitors (%).

Effect	Sildenafil [62–65]	Tadalafil [56, 66, 67]	Vardenafil [68, 69]	Avanafil [70]
Headache	8.1–9.3	8.0–21	5–11	11.5
Flushing	7.4–8.1	3.0–9.0	5.4–10	4
Back pain	2.5	4.6–9.0	0	1
Dyspepsia	2.7–3.0	4.1–17	2.3	3
Nasal congestion	2.7–4.1	2.0–5	10	3
Dizziness	2.5	1.6		
Diarrhoea	2.5	0.8		
Abnormal vision	1.4	0		1
Muscle cramps	4.1	3–7		0

The prevalence quoted for each adverse effect is for the top dose used in each study.

nicorandil), as the combination can cause profound hypotension. A man taking nitrates seeking treatment for erectile dysfunction can be offered alternatives to PDE5 inhibitors or the nitrates can be stopped or changed to an alternative therapy. Nitrates are a symptomatic treatment with no prognostic implications and so this is possible in most cases, but it should be done in consultation with a cardiologist in all but the most straightforward cases.

Nitrate therapy should not be given within 24 hours of taking sildenafil, avanafil, or vardenafil and at least 48 hours of taking tadalafil. If angina develops during or after sexual activity following the use of a PDE5 inhibitor, the man should be advised to discontinue any sexual activity and to stand up, as this reduces the work of the heart by reducing venous return.

PDE5 inhibitors should be used with caution in men who take α-blockers because the combination may lead to symptomatic hypotension in some men. The individuals should be stable on α-blocker therapy before initiating a PDE5 inhibitor at the lowest dose [77].

How to use phosphodiesterase type 5 inhibitors

These agents should be taken orally about one hour before sexual activity. This period can be shortened if the drug is taken on an empty stomach. After the one-hour period, there is a *window of opportunity* when sexual activity can take place. For sildenafil, avanafil, and vardenafil, this is at least four hours, but it may be over eight hours [77]. For tadalafil, the window of opportunity may last 48 hours. Men with diabetes usually require the maximum recommended dose and should be advised that the drug only works in conjunction with sexual stimulation.

Tadalafil can be prescribed as a daily 5 mg dose rather than on an as-required basis. Many men find this more acceptable as it obviates the need to *plan for sex*. It is effective when taken in this way [81] and may be slightly more effective than as-required tadalafil [82], but it is more expensive.

Management of non-responsiveness of phosphodiesterase type 5 inhibitors

It is difficult to predict whether a man will respond to a PDE5 inhibitor. Failure to respond is more likely in men with long-standing and severe erectile dysfunction [37,45]. However, no single factor precludes a successful outcome, and in practical terms it is worth trying a PDE5 inhibitor in all men with erectile dysfunction unless there is a contraindication. It is important that men are advised on how to take their medication properly. Intercourse success rates reach a plateau after eight attempts, so men should try at least eight times with a PDE5 inhibitor at the maximum recommended dose before being considered a non-responder [83].

Even with the maximum dose taken correctly, a large proportion of men with diabetes will not respond to PDE5 inhibitors. Treating any underlying hypogonadism may improve the outcome in this situation, but most men should be offered an alternative treatment.

Hypogonadism

The relationship between diabetes, metabolic syndrome, and hypogonadism has been the subject of considerable interest in recent years. The combination of overweight, sexual dysfunction, fatigue, and borderline low serum testosterone in a middle-aged man with type 2 diabetes is a common clinical problem. The term *late-onset male hypogonadism* has been coined to describe this condition. Pharmaceutical companies have been quick to promote research in this area as they look to widen the market for testosterone products. Reduced serum testosterone is more common in men with the metabolic syndrome and type 2 diabetes [84,85]. Conversely, hypogonadism is associated with a near doubling of the risk of diabetes [86]. However, a causal relationship between the two has not been established and there are many confounding factors. The US Endocrine Society Clinical Practice Guidelines offer clear advice on the management of hypogonadism. It should only be treated if there are symptoms associated with hypogonadism (such as erectile dysfunction) and unequivocal biochemical evidence of hypogonadism [87,88]. There is certainly insufficient evidence to support treating hypogonadism to improve glucose tolerance or cardiovascular risk.

However, a serum testosterone should always be measured in men with diabetes and erectile dysfunction, particularly in those who do not respond to PDE5 inhibitors. Hypogonadism due to confirmed pituitary or testicular disease may be an uncommon finding in this situation, but it usually responds well to treatment with testosterone. In the more common group of men with late-onset male hypogonadism, testosterone replacement may improve erectile dysfunction as a sole treatment [89] and enhance the response to PDE5 inhibitors [90,91].

Other oral therapies

Various oral agents have been tried as treatments for erectile dysfunction in the past, including apomorphine, trazodone, yohimbine, and phentolamine. The data on all of them are limited and none has stood the test of time. They have been supplanted by the PDE5 inhibitors and probably have little role in the management of erectile dysfunction in diabetes.

Intracavernosal injection therapy

Intracavernosal self-injection using phentolamine was first described in 1983 by Brindley [92], although the French urologist Virag [93] reported the use of papaverine slightly earlier. Although papaverine was more effective than phentolamine, it was an unlicensed treatment and was superseded by alprostadil (prostaglandin E), which was licensed for the treatment of erectile dysfunction in 1996.

Alprostadil is supplied in a self-injection pen device, which is easy to use (Figure 54.4). Most studies show that self-injection therapy has a disappointingly high long-term discontinuation rate [94–96]. Self-injection treatment carries a small risk of priapism (a sustained unwanted erection). Although an infrequent complication, priapism is important, as it must be treated within six hours by aspirating blood from the corpus cavernosum. Men undertaking self-injection must be warned of this potential problem and given instructions on what to do should it occur (Box 54.6).

Figure 54.4 Alprostadil self-injection pen device.

Box 54.6 Instructions to medical staff for treating prolonged erections due to prostaglandin E_1

Do not delay treatment beyond six hours.

Using an aseptic technique, aspirate 20–25 ml of blood from the corpus cavernosum (19- or 21-gauge butterfly needle) Repeat this on the opposite side of the penis if detumescence does not occur.

If still unsuccessful, inject 0.5–1.0 ml of a 300 g/l solution of phenylephrine every 5–10 min (maximum dosage 5 ml) into the corpus cavernosum. If necessary, this may be followed by further aspiration of blood through the same needle. Extreme caution is necessary in men taking monoamine oxidase inhibitors, as a hypertensive crisis may result. Use carefully in those with coronary heart disease, uncontrolled hypertension, or cerebral ischaemia. Monitor pulse rate and blood pressure throughout.

If this is unsuccessful, refer for urgent surgical treatment, such as a shunt procedure.

Transurethral alprostadil

Many men find injection therapy unacceptable because it requires injecting the penis, and transurethral administration of the vasoactive agent appears largely to overcome this problem. The principle is simple: a slender applicator is inserted into the urethra to deposit a pellet containing alprostadil in polyethylene glycol. This gradually dissolves, allowing the prostaglandin to diffuse into the corpus cavernosum. In a placebo-controlled study of 1511 men with erectile dysfunction of mixed aetiology, 65% were able to have intercourse using this system [97]. The results in the 240 men with diabetes in the study were similar [98]. Penile pain was reported in 10.8% and hypotension in 3.3% of the men receiving alprostadil. Priapism and penile fibrosis were not reported. As with most non-oral erectile dysfunction treatments, long-term usage has been disappointing [99].

Topical alprostadil cream

Alprostadil is also available as a cream, which is applied around the urethral meatus. It contains dodecyl 2-*N*,*N*-dimethylaminopropionate, a novel penetration enhancer to allow the prostaglandin to reach the erectile tissue. Published data are limited, but it seems to be well tolerated and as effective as transurethral alprostadil [100].

Vacuum therapy

Vacuum devices became widely available in the 1970s. They comprise a translucent tube, placed over the penis, and an attached vacuum pump (Figure 54.5). Air is pumped out of the tube and the negative pressure draws blood into the erectile tissue, producing tumescence. A constriction band (which has previously been placed over the base of the tube) is slipped off to remain firmly around the base of the penis to maintain the erection, and the tube is removed. The devices require some practice and dexterity, but most couples use them satisfactorily. Trials of vacuum therapy have reported success rates of ~70% in men both with and without diabetes, suggesting that it is an effective treatment, provided that couples are prepared to use it [101–103].

Vacuum devices are safe and effective treatments, and inexpensive to use after an initial outlay (in the UK) of ~£100–250. The side effects are discomfort from the constriction band, failure to ejaculate, and a cold penis. Many couples find the use of vacuum devices unacceptable, and since the introduction of newer treatments their use has declined. They still have a role, however, in men who do not respond or who cannot use other treatments. Vacuum devices have the advantage over other erectile dysfunction treatments that they do not need repeat prescriptions and visits to a pharmacist for continued use.

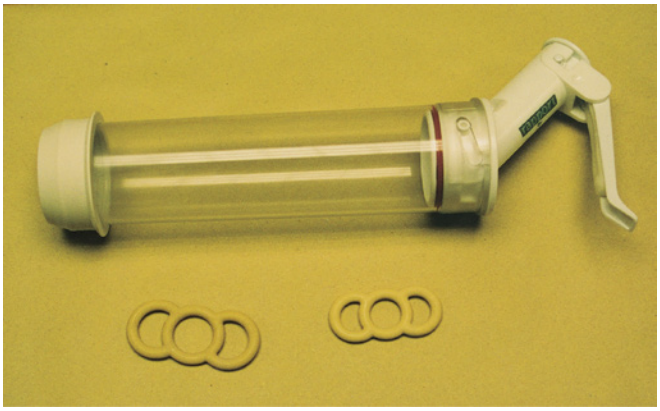

Figure 54.5 Typical vacuum device with constriction rings.

Surgery

In spite of recent advances in the management of erectile dysfunction, some men will not be able to use the available treatment options. There will therefore always be a limited role for surgery.

The surgical options available are as follows:

- Insertion of penile prostheses.
- Corrective surgery for associated Peyronie's disease or post-injection corporal fibrosis.
- Venous and arterial surgery.

Discussion of vascular and corrective surgery of the penis is best left to a specialist urology textbook, but a general practitioner or diabetes healthcare professional needs to know which men might benefit from referral for insertion of a penile prosthesis. This form of surgery is best reserved for those in whom conventional treatments have failed and who are keen to resume full sexual activity.

Counselling of the man, and whenever possible his partner, is important, particularly about the choice of prosthesis. The man's or couple's wishes are important factors in device selection, as is the cost of the prosthesis. Men must be warned regarding postoperative pain or discomfort and the potential need for reoperation. They will need to restrict physical activity and refrain from intercourse for 4–6 weeks after the operation. They should be warned about the possible complications of infection, erosion, and prosthesis failure, and that these problems usually require device removal. It is also important that the man and his partner are aware that the erection produced by a prosthesis is different from a normal erection, depending very much on the type of prosthesis chosen. It is useful to show examples of the prostheses and to describe how they are inserted and the mechanism of action.

There is uncertainty as to whether men with diabetes are at higher risk of infection than those without diabetes after insertion of a penile prosthesis, but there is a consensus that, should infection occur, it is more serious [104]. Good preoperative diabetes management is important to minimize the risk. Most published series of well-selected groups of men who have undergone penile prosthesis

insertion have reported acceptable results, with good levels of patient satisfaction [105].

Organization of the management of erectile dysfunction

Traditionally, erectile dysfunction was managed in a dedicated clinic, often run by a urologist. The advent of effective oral therapies has made the management much simpler, so that erectile dysfunction in diabetes can usually be managed by any diabetologist or general practitioner. A physician considering treating erectile dysfunction will have to decide whether to run a separate clinic or to see the men in a routine diabetes clinic. Such a decision will depend on local resources and circumstances, but it is certainly possible to manage erectile dysfunction in a diabetes clinic. If this is to be done, it is advisable to have information literature on erectile dysfunction available for men with diabetes. A great deal of useful patient information is produced by pharmaceutical companies and national diabetes organizations such as Diabetes UK, both in printed form and online. It is often wise to let the man read this and to consider the matter, with treatment being started at a subsequent visit.

Managing erectile dysfunction in primary care

There are considerable advantages to the treatment of erectile dysfunction in primary care. A general practitioner is more likely to know and understand a man's particular circumstances. Men may feel more comfortable seeking help from their family practitioner than from a hospital specialist or sexual therapist. Little specialized equipment is required, and so there is no reason why interested general practitioners should not effectively treat the majority of men presenting with erectile dysfunction.

As with many disorders encountered in primary care, the general practitioner may choose to manage the problem in a standard consultation with the man. Others may choose to refer their individuals with diabetes to a fellow partner or colleague with a particular interest in erectile dysfunction or to their practice nurse, who may have received appropriate training in the assessment of men with erectile dysfunction.

When a man presents with erectile dysfunction, there is an opportunity to consider other health issues and screen for underlying causes. Erectile dysfunction is often associated with conditions that benefit from early detection such as diabetes, hypertension, and hyperlipidaemia. It is therefore important to consider general health issues and to address lifestyle factors.

Specialist erectile dysfunction service

Although most men with erectile dysfunction will be managed in primary care, there is still a role for a specialist service. It is likely that these clinics will mainly treat men who have failed to respond to oral therapies and that they will maintain expertise in the use of other treatments, such as intracavernosal injection therapy and vacuum devices, referring the men when necessary to urological surgeons for penile prosthesis insertion. Many specialist clinics are run by specialist nurses.

Female sexual dysfunction

Female sexual dysfunction is a common problem and is associated with a range of biopsychosocial factors. Diabetes is a known cause of sexual dysfunction in women, but this is rarely discussed in diabetes consultations.

Physiology of sexual function

The female sexual response has a cognitive and emotional response as well as a physical response [106]. These are reflected in the four phases of the sexual response proposed by Masters and Johnson in 1966 [107]. Physical response involves increased blood flow to the genital region; increased heart rate, blood pressure, and respiration; vaginal lubrication; and nipple erection. Female genitalia refer to the external structure of the vulva, which includes the mons pubis, clitoris and bulbs, labia majora, and labia minora (Figure 54.6) [108]. The internal genitalia includes the vagina. The glans clitoris is visible externally, but the clitoris extends internally and the clitoral bulbs surround the urethra and extend around the vaginal walls. The structure of the genitalia includes two distinct vascular tissues:

- Erectile tissue similar to male genitalia in the clitoris and clitoral bulbs, which engorge with blood during sexual arousal.
- Non-erectile vascular tissue in the glans clitoris and labia minora.

The walls of the vagina enlarge with increased blood flow during sexual arousal, but also comprise non-erectile tissue. For normal sexual response there needs to be adequate blood supply to the external and internal genitalia, together with normal function of the sensory and autonomic nervous system. Clitoral erectile tissue function is dependent on the NO/cGMP pathway in the same way as erectile function is governed in men [109].

The first of stage of the sexual response is desire, and the second is arousal. However, women may not experience distinct phases [110]. Arousal can be induced both mentally and physically, and can involve all the senses either individually or in combination. The third stage is orgasm, although there is a lack of consensus as to how this is induced and its involvement in reproductive fitness, male and female satisfaction, and brain activity involvement. The final stage is resolution or satisfaction.

Physiology of sexual dysfunction

Sexual activity is associated with multiple health benefits, such as improved quality of life, quality of social relationships, and mental well-being, and it is a good form of exercise. However, female sexual dysfunction is common and affects women of all ages [111, 112]. In physiological terms, female sexual dysfunction may occur because of reduced vasocongestion of the vulva and vagina, leading to impaired arousal and reduced vaginal lubrication. According to the World Health Organization [113], there are four categories of female sexual dysfunction: sexual desire disorder, sexual arousal disorder, orgasmic dysfunction, and sexual pain disorder. However,

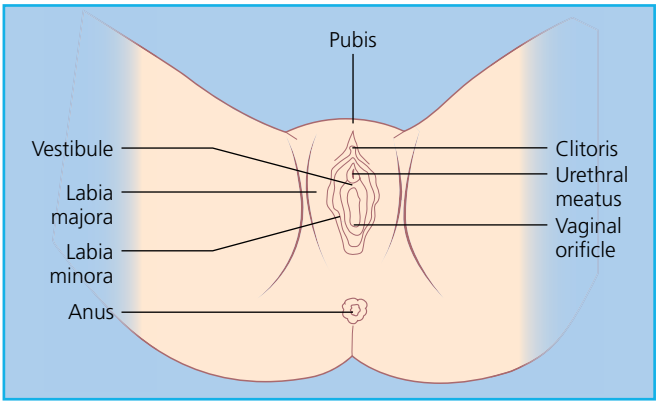

Figure 54.6 Female genitalia.

the fifth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [114] reduced these to three by combining the first two:

- *Female sexual interest/arousal disorder*: a lack of sexual interest or failure to become aroused.
- *Female orgasmic disorder*: difficulty achieving orgasm.
- *Genito-pelvic pain/penetration disorder*: dyspareunia or vaginismus.

For diagnosis of these specific categories of sexual dysfunction, each should be present for 75–100% of the time and for a minimum period of six months and cause significant distress. The three categories of sexual dysfunction are largely consistent with the International Classification of Diseases 11 (ICD-11) and the Fourth International Consultation on Sexual Medicine (ICSM) is consistent with DSM-5 [115, 116]. Some female sexual disorders may overlap and the exact cause may be difficult to distinguish, as it can incorporate psychological, interpersonal, and physical factors [117].

The factors affecting sexual dysfunction were summarized by Khajehei et al. [118], who suggest five categories:

- Medical-surgical conditions, e.g. lower urinary tract problems, voiding problems, endometriosis, diabetes.
- Obstetrics and gynaecology, e.g. childbirth, breastfeeding, menopause, hysterectomy.
- Psychological, e.g. depression, anxiety, mental health problems.
- Lifestyle, e.g. physical activity, smoking, alcohol and drug use.
- Other factors, e.g. sexual orientation, practice, abuse, negative body image.

However, other associated factors suggested by DSM-5 and ICD-11 not listed here can include relationship or partner factors (Box 54.7).

Pathophysiology of female sexual dysfunction in diabetes

Women with diabetes are at increased risk of sexual dysfunction, but prevalence rates vary between studies. In premenopausal women with type 1 diabetes prevalence rates are 20–44% [119–123] and in mixed pre- and postmenopausal studies of women with type 1 diabetes rates are 42% [122]. For postmenopausal women with type 2 diabetes rates are also high, at 42–75% [122]. Compared with women without diabetes, women with type 1 diabetes or type 2 diabetes are twice as likely to have sexual dysfunction, as demonstrated in a systematic review and meta-analysis of 26 observational studies [124]. Women with diabetes and higher body mass index (BMI) are also more likely to report sexual dysfunction when measured by the validated self-report Female Sexual Function Index (standardized mean difference [SMD] −0.90, 95% CI −1.00 to −0.81) [124]. In women with type 1 diabetes, Enzlin et al. demonstrated that those who met the cut-off for depression on the Beck Depression Inventory were at greater risk of sexual dysfunction [125].

For women with diabetes, high or low blood glucose levels are associated with reduced vaginal lubrication, painful sex, and inability to orgasm [126, 127]. High rates of depression, known to be double that of general population samples [46], also have an impact on sexual function. Issues related to body image and scarring, injection sites, or wearing of medical devices may affect confidence to engage in sexual activity [128]. Furthermore, diabetes-related fatigue, fear of hypoglycaemia during sex, and the need to test blood glucose levels frequently may add to the general inconvenience of self-managing diabetes and maintaining sexual activity [129]. Such issues are all likely to affect relationships with a partner [130].

Box 54.7 Conditions associated with female sexual dysfunction

Psychological disorders
Anxiety
Depression
Stress
Obsessive compulsive disorder
Psychiatric problems
Fear of childbirth
Fear of sexually transmitted disease

Gynaecological trauma
Sexual abuse
Genital mutilation
Trauma caused by childbirth
Menopause
Hormonal imbalance
Hysterectomy
Ovariectomy
Endometriosis
Uterine fibroids

Urological conditions
Painful bladder symptoms
Lower urinary tract problems
Urinary incontinence
Leakage of urine during sexual activity

Social factors
Relationship factors
Age

Neurological disorders
Spinal cord injury
Multiple sclerosis

Endocrine and metabolic disorders
Diabetes
Hypothyroidism
Hypopituitarism

Lifestyle
Physical activity
Smoking
Drug abuse
Alcohol abuse

Other medical conditions
Hypertension
Cancer
Inflammatory disease

Clinical aspects of sexual dysfunction for women with diabetes

There is a general consensus that failure of arousal is more common, occurring in 14–45% of women with diabetes [125, 131]. In contrast, studies have reported conflicting results on the prevalence of orgasmic disorder [125, 132] and genito-pelvic pain in diabetes [126]. It would be reasonable to summarize the results of all the studies by saying that sexual dysfunction is

more common in women with diabetes and is mainly characterized by failure of arousal, although orgasmic problems and dyspareunia may also occur.

Sexual dysfunction as a risk factor for cardiovascular disease in women with diabetes

In women with diabetes, sexual dysfunction is emerging as a risk factor for cardiovascular disease via its impact on autonomic neuropathy. The main evidence for this comes from the 16/17-year follow-up of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. Among 153 women with type 1 diabetes and sexual dysfunction, there were increased odds of developing cardiovascular autonomic neuropathy (CAN) (odds ratio [OR] 1.52, 95% CI 0.89 to 2.61) [133].

Atherosclerosis may be relevant to sexual function in women with diabetes. Clitoral colour Doppler ultrasound is a novel technique to assess the pulsatility index (PI), which measures the resistance to blood flow in the vascular structures and increased resistance and suggests micro-atherosclerosis. Clitoral colour Doppler ultrasound was used to measure sexual functioning in a clinic population of 71 women seeking treatment. Clitoral PI was statistically higher in women who were obese or had metabolic syndrome after adjustment for confounders [134]. Clitoral PI markers of metabolic syndrome, specifically degree of insulin resistance (higher homeostasis model assessment [HOMA] index) and triglyceride levels, were associated with increased PI. Increased clitoral PI was also associated with reduced arousal on the Female Sexual Function Index domain. Similar findings might be anticipated in a population of women with type 2 diabetes. The lack of research in this area means that we do not know if treatment can improve clitoral PI or if PI can be used to predict cardiovascular events.

Sexual dysfunction and peripheral neuropathy in women with diabetes

Sexual dysfunction, such as problems with orgasm and vaginal lubrication, is associated with central nerve damage, as in spinal cord injury. Sensory or peripheral nerve damage may also be a problem for women with diabetes. There is an increased incidence of sexual dysfunction for women who have diabetes-related peripheral neuropathy [135]. Women with diabetes demonstrate less physiological arousal compared with those without diabetes when viewing erotic stimuli [136]. Similarly, sensation in the vagina and clitoris is reduced in women with diabetes [137].

Smoking and alcohol consumption

Although smoking and alcohol consumption are associated with erectile dysfunction in men with diabetes, there is no evidence of an association for women with type 1 diabetes or type 2 diabetes. In a cross-sectional study of 524 women with diabetes in Jordan, sexual dysfunction was associated with age, BMI, duration of diabetes, presence of coronary artery disease, nephropathy, and retinopathy, but not directly with smoking [138].

Quality of life and psychological issues

In a study of 595 women with type 2 diabetes, depression, defined as antidepressant use or prior psychological counselling for depression, was independently associated with sexual dysfunction on the Female Sexual Function Index [139]. Furthermore, in a study by Enzlin et al. [125], women with type 1 diabetes who reached the cut-off for depressive symptoms on the Beck Depression Inventory were four times more likely to have sexual dysfunction (37.7% vs 8.3%, $p<0.001$). More recently, Barnard et al. [44] replicated a survey study originally conducted by Meeking et al. 1998 [140], with a population of 258 women with diabetes recruited via social media. More than 50% of the sample had problems with painful sex and orgasm. Free text responses indicated that diabetes had a negative impact on relationships with a partner, including lack of sexual interest [44].

Assessment and investigation of sexual dysfunction in diabetes

Clinical assessment

Female sexual dysfunction is rarely discussed in the diabetes clinic. Women rarely complain of sexual dysfunction and may not know that diabetes is a cause. Furthermore, women may feel embarrassed to discuss sexual issues, and diabetes healthcare professionals may also be unaware of the association with diabetes and/or feel ill-equipped to raise the topic. One way to identify the issue in a routine consultation could be to use self-report questionnaires or clinician checklists. The validated 19-item Female Sexual Function Index determines sexual function according to six domains including: sexual desire, arousal, lubrication, orgasm, satisfaction, and dyspareunia (pain) [141]. It is scored on a five-point scale, with higher scores indicating less sexual dysfunction. Shorter measures include the Brief Sexual Symptom Checklist for women (BSSC-W). Measures such as these may form the basis of more detailed discussion within the clinical setting [142].

Investigation of sexual dysfunction

Formal investigation of sexual dysfunction once identified should involve detailed medical history taking, including medical, physical, and psychological factors. It is important to determine prior sexual abuse, genital mutilation, or trauma caused by childbirth. Physical examination should be conducted by a gynaecologist. Review of medications to identify those that may exacerbate sexual function (Box 54.8) and screening of depression, anxiety, and body image are important. Blood tests may identify underlying disorders in addition to diabetes diagnosis, for example prolactin and testosterone to determine low/high levels of circulating sex hormones and thyroid function test to determine an additional underlying endocrine cause.

General advice

Women with diabetes rarely complain of sexual problems and diabetes health professionals rarely ask. In physiological terms, the female equivalent of male erectile dysfunction is reduced vasocongestion of the vulva and vagina, leading to impaired arousal and reduced vaginal lubrication. Failure to achieve an erection makes sexual intercourse impossible, but reduced vaginal lubrication can be overcome with simple treatments such as lubricating creams and may not even be considered to be abnormal by a postmenopausal woman. However, women may be suffering in silence and diabetes healthcare professionals may need to acquire skills to enable them to start the conversation. Optimization of blood glucose levels may improve symptoms of sexual dysfunction and this is therefore an important first step to support women. Other diabetes-related issues such as those to do with body image or the inconvenience of managing diabetes to maintain a sexual relationship might also be best discussed within a diabetes consultation, and will only happen if healthcare professionals are proactive in discussing the topic with women.

Box 54.8 Medications associated with female sexual dysfunction

Antihypertensives
β-blockers
Thiazide diuretics
Central sympatholytics (methyldopa, clonidine)
Aldosterone receptor agonists

Antidepressants
Selective serotonin reuptake inhibitors (SSRIs)
Monoamine oxidase (MAO) inhibitors
Tricyclic antidepressants

Antipsychotics
Barbiturates
Benzodiazepines
Lithium

Hormones
Danazol
Gonadotrophin-releasing hormone (GnRH) agonists
Hormonal contraceptives
Anti-androgens
Tamoxifen
Gonadotrophin-releasing hormone (GnRH) analogues

Miscellaneous
Statins
Anticholinergics
Antihistamines
Digoxin
Chemotherapeutic agents

Substance misuse
Smoking
Amphetamines
Opiates

Treatment options

There is limited research on treatment of sexual dysfunction in women with diabetes. Most research has focused on pharmacotherapy, specifically PDE5 inhibitors and bupropion, an atypical antidepressant (norepinephrine-dopamine reuptake inhibitor, NDRI). PDE5 inhibitors have been tested in premenopausal women with type 1 diabetes with sexual arousal disorder, and demonstrated subjective improvements in arousal, desire and enjoyment of sexual activity, and objective measures of clitoral blood flow [143]. PDE5 inhibitors have not been tested in women with type 2 diabetes, although they have been used to treat pulmonary hypertension [144]. There is a single study suggesting that bupropion may improve sexual dysfunction in women with type 2 diabetes who were depressed [145]. However, there are no licensed treatments for women with diabetes and sexual dysfunction.

Psychological interventions

There are no published studies of psychological interventions for women with diabetes and sexual dysfunction. However, a systematic review and meta-analysis of 15 studies of women without diabetes with sexual dysfunction demonstrated improvements in orgasmic disorder (d = 0.46, 95% CI 0.07 to 0.86) [146].

Organization of the management of sexual dysfunction

Female sexual dysfunction if identified can be managed in a dedicated clinic, but this is currently not generally offered in the diabetes clinic. Nevertheless, it may be possible to offer a service to women and some UK National Health Service (NHS) services have successfully integrated a discussion of sexual dysfunction into clinics with support from a diabetes psychotherapy service [147]. There are now a few useful patient information leaflets that could be made available to women and may prompt them to discuss their issues within their diabetes consultation. For example, more information and/or leaflets can be found on the webpages for Diabetes UK and Diabetes Health and Wellness Foundation [127].

Management of female sexual dysfunction

Many women attending a diabetes clinic will be over 50 years of age and some will have problems associated with the menopause, including vaginal dryness and dyspareunia. It can be difficult to distinguish the effects of the menopause from those of diabetes, but in practical terms the treatment is the same. Topical oestrogen or simple lubricant gels are usually effective. Managing loss of libido in women with diabetes is more complex and beyond the scope of this book. It is much more likely to be due to psychosocial and relationship, rather than somatic, problems. Similarly, anorgasmia is complex and best left to a specialist, although it is worth remembering that selective serotonin reuptake inhibitor antidepressants are a common cause.

The mechanism of action of PDE5 inhibitors suggests that they might improve arousal and vaginal lubrication. However, trials of PDE5 inhibitors for this purpose in women with and without diabetes have shown conflicting results. Measures of genital vasocongestion and clitoral blood flow have been reported to improve, but the impact on self-reported measures of sexual satisfaction has been disappointing [148, 149]. PDE5 inhibitors probably have little role in the management of sexual dysfunction in women with diabetes.

For postmenopausal women and sexual dysfunction, tibolone is a systemic hormone replacement therapy (HRT) that has demonstrated an improvement in sexual dysfunction on the Female Sexual Function Index, specifically improved vaginal lubrication and reduced dyspareunia [150, 151]. Tibolone is a synthetic steroid that has similar function to progesterone, oestrogen, and testosterone.

Genitourinary infections in women with diabetes

Vaginal candidiasis is a common finding in women with diabetes if there is hyperglycaemia, because yeasts thrive in a glucose-rich environment. Severe infection can be irritating, painful, and can interfere with sexual intercourse. Infections typically respond to conventional antifungal creams and pessaries; resistant cases usually respond to a single oral dose of fluconazole. To reduce chance of reinfection, attempts should be made to optimize blood glucose levels. The male partner may also need treatment for candidiasis for the same reason.

Other genital infections also occur in women with diabetes, but probably no more frequently than in the general population. These cases should be referred to the appropriate genitourinary service.

Contraception

Contraception and family planning are especially important in women with diabetes. Suboptimal glycaemic levels during the first

trimester of pregnancy is associated with an increased risk of fetal morbidity and mortality [152–155]. It is essential that women with diabetes are supported to plan their pregnancies with diabetes prior to conception (Chapter 71).

Contraindications to pregnancy

As medical and obstetric care has improved, the list of contraindications to pregnancy in women with diabetes has shrunk (Chapter 71). If pregnancy is contraindicated, sterilization should be considered.

Method of contraception

Few diabetes organizations make any recommendation on the preferred method of contraception to be used in women with diabetes. The American Diabetes Association's recent Standards of Medical Care in Diabetes recommend that effective contraception is particularly important, but the options and recommendations are largely the same as those for women without diabetes [156]. This is true, but certain factors, in particular impact on risk factors and carbohydrate tolerance, should be taken into consideration before choosing any particular method.

Hormonal contraception

The oral contraceptive pill (OCP) remains one of the popular methods of contraception in women with diabetes in high-income countries [157]. It is simple to use and reliable. If properly used, it has the lowest failure rate for any contraceptive method, apart from sterilization [158]. Unfortunately, OCPs are associated with female sexual dysfunction, specifically arousal problems [159]. Long-acting reversible contraceptives are now recommended as first line for adolescents and young women by the American College of Obstetrics and Gynaecologists [160] and the American College of Paediatrics [161], whereas the UK National Institute of Health and Care Excellence (NICE) guidance refers to individual choice [162]. There is no evidence on their use in adolescents with diabetes [163] and there have been concerns about the safety of hormonal contraception in women with diabetes.

Hormonal contraception, carbohydrate tolerance, micro- and macrovascular risk

There is no evidence that hormonal contraceptives affect carbohydrate tolerance or metabolic management in women with diabetes. A Cochrane review of studies examining the impact of steroidal contraception in women without diabetes reported that there was minimal impact on carbohydrate metabolism and no major differences between different types of hormonal contraceptives [164]. In women with type 1 diabetes or type 2 diabetes, a more recent Cochrane review reported that neither combined nor progestin-only contraceptives had a significantly different effect than non-hormonal contraception on glucose levels, lipid metabolism, or complications [165]. A small impact of hormonal contraception on glucose levels cannot be ruled out, but in practical terms this should not deter their use in women with diabetes.

The cardiovascular safety of hormonal contraception is not beyond doubt, because most reported studies were flawed or small and a large definitive study examining the effects on cardiovascular morbidity and mortality in women with diabetes is needed. When considering prescribing hormonal contraception to a woman with diabetes, the same factors should be considered as in a woman without diabetes. Smoking, hypertension, age, and vascular disease should be considered and the risks weighed for the individual woman. The World Health Organization's published criteria for contraceptive use provide useful practical advice on the choice of contraception in women with diabetes [166].

Once the risks have been assessed, any combined or progestin-only contraceptive can be used in women with type 1 diabetes or type 2 diabetes and the individual's preference should be considered. Any woman taking hormonal contraception should be reviewed regularly for assessment of blood pressure and serum lipids.

Combined hormonal contraceptive preparations carry an increased risk of venous thromboembolism. The risk is probably greatest (50–80% increase) with the *third-generation* progestins, desogestrel and gestodene, compared with preparations containing levonorgestrel [167]. The risk remains very small, however, and these are still safe preparations. There is no evidence that progestin-only contraceptives are associated with an increased risk of thrombosis.

Intrauterine contraceptive device

The intrauterine contraceptive device (IUD) is a safe and effective form of contraception in women with diabetes. Early concerns about the risk of pelvic inflammatory disease in diabetes were largely unfounded, with no increased risk of pelvic inflammatory disease in women with type 1 diabetes [168] or type 2 diabetes [169]. Similarly, early suggestions of an increased failure rate for IUDs in women with diabetes have not been borne out [168].

Barrier methods

Since the advent of acquired immune deficiency syndrome (AIDS), the condom has been widely advocated to reduce the risk of transmission of sexually transmitted diseases. It has a higher failure rate than OCPs and IUDs and for this reason is not recommended if pregnancy is contraindicated. For high-risk individuals, many genitourinary clinics recommend a combination of the OCP and condoms to minimize the risk of pregnancy and sexually transmitted diseases, a technique known as *double Dutch*.

Emergency contraception

Three methods of emergency contraception are licensed in the UK and are available in many other countries: progestogen-only and combined oestrogen–progesterone pills, and the copper IUD. The hormonal preparations can be taken up to 72 hours after unprotected intercourse, but are most effective if taken within 24 hours [170]. Nausea was reported in 23% and vomiting in ~6% of the women who used the progesterone-only regimen. Women with type 1 diabetes should be warned of these potential side effects. Little work on the use of these agents in women with diabetes has been published, but they may have a role in the prevention of unplanned pregnancies occurring at a time of hyperglycaemia.

Hormone replacement therapy

Few areas of medicine have gone through as many changes in perception in modern times as HRT. It was used as a treatment for osteoporosis and menopausal symptoms, but had become regarded as a potential treatment to reduce cardiovascular risk, largely based on observational studies. In 2001, a survey of general practitioners and hospital doctors in the UK suggested that the majority would advise HRT for women with diabetes as prophylaxis for cardiovascular disease [171]. Attitudes changed almost overnight, however,

following the publication of the Women's Health Initiative trial in 2002 [170]. This was a large, randomized study of combined oestrogen and progesterone HRT that was stopped early because of increased adverse outcomes, including cardiovascular disease, stroke, thromboembolism, and breast cancer. Further evidence has accumulated and now HRT is viewed largely as a short-term treatment for menopausal symptoms that does not increase cardiovascular risk, but is not without risk. Many women with diabetes are postmenopausal, and so diabetes professionals need to be aware of the potential risks and benefits.

Hormone replacement therapy and glucose tolerance

HRT does not worsen glucose tolerance in women with or without diabetes and may produce a slight amelioration. In women without diabetes, oestradiol and low-dose conjugated oestrogens are associated with an improvement and no effect on insulin sensitivity, whereas higher doses of conjugated oestrogens and alkylated oestrogens may cause deterioration of glucose tolerance [173–175].

In postmenopausal women with diabetes, oestradiol improves the fasting blood glucose concentration and glycated haemoglobin [176]. A larger observational study of over 15 000 women with type 2 diabetes also reported that HRT was associated with an improvement in glycated haemoglobin (HbA_{1c}) [177]. The NICE guideline for the treatment of the menopause concluded that there was no adverse effect or benefit on fasting blood glucose or HbA_{1c} at three or six months' follow-up for women with type 2 diabetes treated with HRT [178]; however, as the five studies had a small sample size, the evidence was deemed low to very low quality. A Cochrane review concluded that there is little or no evidence for women with type 1 diabetes [179].

Hormone replacement therapy and lipids

Like glucose tolerance, the effect of HRT on lipid profiles appears to be at worst neutral and may be slightly beneficial. In women without diabetes, oestrogens reduce total and low-density lipoprotein (LDL) cholesterol and increase high-density lipoprotein (HDL) cholesterol and triglyceride levels [180,181]. Transdermal oestrogen preparations have a beneficial effect on plasma lipids, reducing LDL cholesterol and triglycerides and increasing HDL cholesterol [181].

The effect of HRT on lipid profiles in women with diabetes has been reported in several studies. In a small, randomized crossover study of women with overweight and type 2 diabetes, conjugated oestrogen therapy reduced central obesity, HbA_{1c}, and total cholesterol, and improved physical functioning [183]. In another small, randomized crossover study, conjugated oestrogens reduced total and LDL cholesterol and increased HDL cholesterol in women both with and without diabetes. The addition of medroxyprogesterone acetate abolished the increase in HDL in both groups. There was no apparent effect on fasting glucose or insulin levels [184]. In the largest study, 61 postmenopausal women received combined HRT in a randomized crossover design. HRT reduced total and LDL cholesterol, but there was no change in serum HDL or triglyceride levels [185].

Hormone replacement therapy and blood pressure

HRT can be prescribed to postmenopausal women with hypertension under careful supervision. One of the few studies of HRT and blood pressure in diabetes suggested that it can be prescribed without any adverse effect on ambulatory blood pressure measurements in hypertensive and normotensive women [186].

Hormone replacement therapy and ischaemic heart disease

Early case–control studies suggested that HRT reduces the risk of ischaemic heart disease in postmenopausal women by 30–50% [187, 188]. Subsequent clinical trials, nevertheless, reported very different results, and a reasonable summary of subsequent studies would be that there is no evidence that HRT reduces cardiovascular risk, but it probably does not increase it [189,190]. It is, however, associated with an increase in thromboembolic disease. No large studies on the effect of HRT on the risk of ischaemic heart disease in women with diabetes have been reported. Therefore, when managing a postmenopausal woman with diabetes, guidance for the general population should probably be followed. Recently published guidance from NICE provides useful practical advice [178]. In brief, HRT should be considered as a short-term treatment for menopausal symptoms. Cardiovascular risk factors are not a contraindication provided that they are adequately managed. Transdermal preparations should be considered if there is a history of thromboembolic disease.

Hormone replacement therapy and osteoporosis

Women with type 1 diabetes have reduced bone mineral density at the time of diagnosis [191]. Although women with type 2 diabetes might be expected to be protected from osteoporosis because of their increased tendency to obesity, they are at increased risk of hip fracture (Chapter 59). A very large prospective cohort study of postmenopausal women in Iowa reported that women with diabetes had a 1.7-fold higher risk of hip fracture than women without diabetes [192]. Hence the benefits of HRT in reducing the risk of osteoporotic fractures would appear to be at least as great in women with diabetes as in those without diabetes, and HRT should be considered for postmenopausal women with diabetes with osteoporosis.

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55 Gastrointestinal Manifestations of Diabetes

Michael Camilleri and Adil E. Bharucha

Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER), Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

Key points

- Diabetic enteropathy refers to all the gastrointestinal complications of diabetes, which can affect the entire gastrointestinal tract.
- Gastrointestinal symptoms in diabetes include dysphagia, dyspepsia, gastroparesis, abdominal pain, constipation, diarrhoea, and faecal incontinence. Some gastrointestinal disturbances (e.g. delayed gastric emptying) are often asymptomatic.
- Although these gastrointestinal symptoms are not uncommon among people with diabetes in clinical practice, the prevalence of gastrointestinal manifestations among such people in the community is not substantially higher than in the general population.
- These gastrointestinal manifestations can reduce quality of life and nutrition and also impair glycaemic management.
- These symptoms are attributed to gastrointestinal sensorimotor dysfunction resulting primarily from extrinsic and intrinsic nerve (i.e. enteric) dysfunction.
- The investigations are tailored to the presenting symptoms and require tests to exclude an organic disorder (e.g. gastric outlet obstruction in gastroparesis), to confirm gastrointestinal sensorimotor dysfunction (e.g. delayed gastric emptying), and to identify complications (e.g. small intestinal bacterial overgrowth).
- The management of gastrointestinal symptoms in diabetes relies primarily upon improving glycaemic management and symptomatic measures, in addition to attention to the individual's state of hydration and nutrition.

Although most attention has traditionally been focused on the stomach, diabetes can affect the entire gastrointestinal tract. The term *diabetic enteropathy* refers to all the gastrointestinal complications of diabetes. Gastrointestinal involvement may be asymptomatic or manifest as symptoms, such as dysphagia, heartburn, nausea, vomiting, abdominal pain, constipation, diarrhoea, and faecal incontinence. These manifestations may affect quality of life, impair nutrition, and affect glycaemic management.

Epidemiology of diabetes-related enteropathy

Studies in selected groups, often from tertiary referral centres, suggest that gastrointestinal symptoms are common in diabetes [1, 2]. However, these studies are prone to selection and other biases, which are avoided by studies conducted among people with diabetes in the community, where the prevalence of gastrointestinal symptoms is either not different from or only slightly higher than for people without diabetes. In the Rochester Diabetic Neuropathy Study, only 1% of people with diabetes had symptoms of gastroparesis and only 0.6% had nocturnal diarrhoea [3]. In another study from Olmsted County, Minnesota, USA, the prevalence of gastrointestinal symptoms (i.e. nausea and/or vomiting, dyspepsia, heartburn, irritable bowel syndrome, constipation, and faecal incontinence) was not significantly different between individuals with either type 1 diabetes or type 2 diabetes and age-matched people without diabetes [4]. However, people with type 2 diabetes and men with type 1 diabetes used laxatives more frequently than people without diabetes. Moreover, that study and a Finnish population-based study reported that people with type 1 diabetes had a lower prevalence of heartburn [5]. In contrast to these studies, a study in Australia found that the prevalence of several upper and lower gastrointestinal symptoms was higher in 423 people with predominantly (95%) type 2 diabetes than in people without diabetes [6].

Compared with those studies, which were anchored by symptoms alone (i.e. not by diagnostic tests), the cumulative 10-year incidence of gastroparesis has been estimated at 5.2% in type 1 diabetes and 1% in type 2 diabetes in a community sample of people with diabetes [7]. In that study, gastroparesis was documented by physician diagnosis based on delayed gastric emptying with scintigraphy, or by symptoms and retained food at endoscopy. However, because gastroparesis was identified only in people who presented for care, people who had an asymptomatic delay in gastric emptying may not have been identified. Hence, the estimated incidence and prevalence of gastroparesis are critically dependent on definition [8].

Studies of the natural history of gastroparesis have been limited by relatively small numbers of participants, potential referral bias, or short follow-up periods. One study suggested that delayed

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gastric emptying and symptoms are both relatively stable over 12 or 25 years [9]. In a clinic-based study, diabetic gastroparesis was associated with severe symptoms, nutritional compromise, impaired glucose management, and a poor quality of life, independent of other factors such as age, tobacco use, alcohol use, or type of diabetes [10]. Several studies have investigated the association between diabetic gastroparesis and mortality or morbidity [11–18]. For example, among 86 people with diabetes, of whom 56% had delayed emptying of solids and 28% had delayed emptying of liquids, ~25% had died by follow-up at least nine years later. Gastroparesis was not associated with mortality after adjustment for other disorders [11]. However, this study did not ascertain the relationship between diabetic gastroparesis and other medical conditions. In another study that compared three parallel cohorts of people with diabetes (i.e. 94 with symptoms and delayed gastric emptying, 94 with classic symptoms of delayed gastric emptying but normal scintigraphy, and 94 with no symptoms of gastroparesis), diabetic gastroparesis was associated with cardiovascular disease, hypertension, retinopathy, and increased hospitalization [12]. Compared with those with gastrointestinal symptoms alone, people with diabetic gastroparesis also had more hospital days; mortality was also greater, but differences were not statistically significant. In the National Institute of Diabetes, Digestive and Kidney Diseases Gastroparesis Clinical Research Consortium, the incident death rate for a cohort of 358 people with gastroparesis was 0.015 deaths per person-year. The death rate was significantly higher in 50 people with type 1 diabetes and 59 with type 2 diabetes compared with idiopathic (n = 249) cases (0.0266 vs 0.0094 deaths per person-year) and in those with delayed (73%) compared with normal (27%) gastric emptying (0.0189 vs 0.0031 deaths per person-year) [19].

Taken together, these data suggest that gastrointestinal manifestations are common among people with diabetes presenting for care. However, in the general population, the prevalence of gastrointestinal manifestations is not substantially higher among people with diabetes, perhaps partly because the prevalence of gastrointestinal symptoms among people without diabetes in the community is relatively high, approaching 20%, mostly attributable to functional gastrointestinal disorders (e.g. irritable bowel syndrome). Among people with gastrointestinal symptoms, the gastric emptying assessment can identify those with a worse prognosis. Whether this increased morbidity is driven by gastroparesis is unknown.

Data on long-term natural history in the community are available from an epidemiology study in the UK [20]. Ye et al. utilized the Clinical Practice Research Datalink (CPRD) database, an anonymized data source of general practitioner records with 4.4 million active patients comprising 7% of the entire UK population and representative in terms of age, sex, ethnicity, and body mass index (BMI) [20]. They estimated an overall prevalence of gastroparesis of 13.8 per 100 000 persons and an incidence of 1.9 per 100 000 person-years [20]. This estimate is comparably lower than a report from Olmsted County, Minnesota, the only other reported population-based study of gastroparesis [21]. In both studies, diabetes-related and idiopathic were the most prevalent forms of gastroparesis. In some [20, 21], but not all [12] studies, mortality appeared to be higher in individuals with both diabetes and gastroparesis. Associated morbidity in those with diabetic gastroparesis (estimated by Charlson morbidity index) was associated with mortality [20], but the relationship of the classical diabetic triopathy (neuropathy, nephropathy, and retinopathy) to gastroparesis or mortality was not assessed.

Pathophysiology

Gastrointestinal dysmotility in diabetes is caused by extrinsic (i.e. sympathetic and parasympathetic) neural dysfunction, hyperglycaemia, and hormonal disturbances. More recently, a role for intrinsic (i.e. enteric) neuronal dysfunction, resulting from loss of excitatory and inhibitory neurons and interstitial cells of Cajal (ICC), has also been implicated [22]. Neural dysfunction has been attributed to several mechanisms (e.g. oxidative stress), described in what follows and detailed elsewhere [23].

Normal gastrointestinal motor functions

Gastrointestinal motor function is primarily controlled by the intrinsic or enteric nervous system (i.e. the 'little brain' in the digestive tract) and modulated by the extrinsic (i.e. parasympathetic and sympathetic) nervous system (Figure 55.1) [25]. While intrinsic and extrinsic controls are independent, the prevertebral ganglia integrate afferent impulses between the gut and the central nervous system and provide additional reflex control of the abdominal viscera. The parasympathetic arm is excitatory to non-sphincteric muscle and inhibits sphincters. The sympathetic component has opposite effects. The enteric nervous system consists of 100 million neurons that are organized in distinct ganglionated plexi, including the submucous plexus that is primarily involved in absorption and secretion, and the myenteric plexus that regulates motility. The ICC serve as pacemakers and also convey messages from nerves to smooth muscle. As with the somatic and autonomic nerves elsewhere, the gut's autonomic and enteric nervous system can be affected in diabetes. Derangements of the extrinsic nerves at any level may alter gastrointestinal motility and secretion [26].

Gastrointestinal digestion and absorption require gastrointestinal motility, gastric and pancreatic secretion, and gastrointestinal hormonal release, which in turn modulate motor, secretory, and absorptive functions in the upper gut [27]. Traditionally, these processes are considered in three phases – that is, cephalic, gastric, and intestinal – which are integrated and overlap. Normally liquids, particularly non-caloric liquids, empty rapidly from the stomach in a linear fashion. In contrast, gastric emptying of solids follows an exponential pattern. During the first 45-minute post-prandial period (i.e. the lag phase), the gastric antrum grinds solids into particles smaller than 2 mm in size so they can be emptied through the pylorus. During the lag phase, the stomach relaxes or accommodates, providing room for digestion to occur (Figures 55.2 and 55.3). Thereafter, solids are emptied in a linear fashion, with ~50% emptying in two hours and 100% emptying in four hours.

Pancreatobiliary secretions and mechanical processes ensure small intestinal digestion, which precedes absorption. The small intestine transports solids and liquids at approximately the same rate; the head of a column of liquid chyme may reach the caecum as early as 30 minutes after ingestion. As a result of the lag phase for the transport of solids from the stomach, liquids typically arrive in the colon before solids. However, it takes about 150 minutes for half the solid and liquid chyme of similar caloric density (assuming solids are presented in a triturated form to the small bowel) to traverse the small bowel. Complex carbohydrates or fat in the distal small intestine exert feedback control of proximal small intestinal motility (i.e. the small intestinal brake). Chyme is transferred from the ileum to the colon in intermittent boluses. On average, it takes 36 hours, with an upper limit of 65 hours, to transfer contents from the caecum to the rectum. Compared with the stomach and small

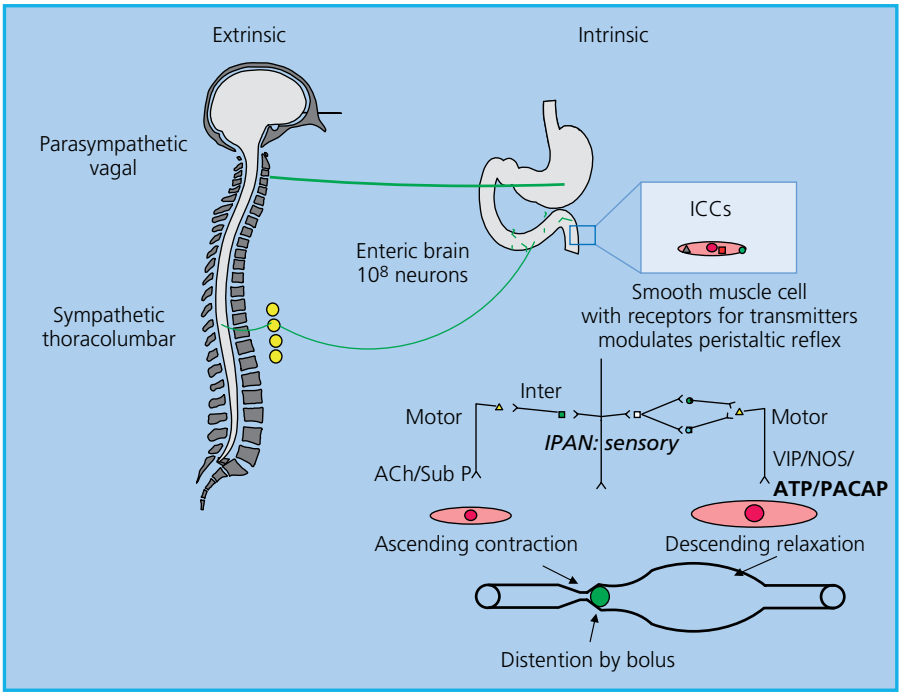

Figure 55.1 Control of gastrointestinal motility. Note that the extrinsic or autonomic nervous system modulates the function of the enteric nervous system, which controls smooth-muscle cells through excitatory (i.e. acetylcholine [Ach], substance P [SubP]) or inhibitory (nitric oxide [NO], vasoactive intestinal peptide [VIP], pituitary adenylate cyclase activating peptide [PACAP]) neurotransmitters. ICCs, interstitial cells of Cajal; IPAN, intrinsic primary afferent neurons; NOS, nitric oxide synthase. Source: Adapted by permission from Camilleri and Phillips 1989 [24].

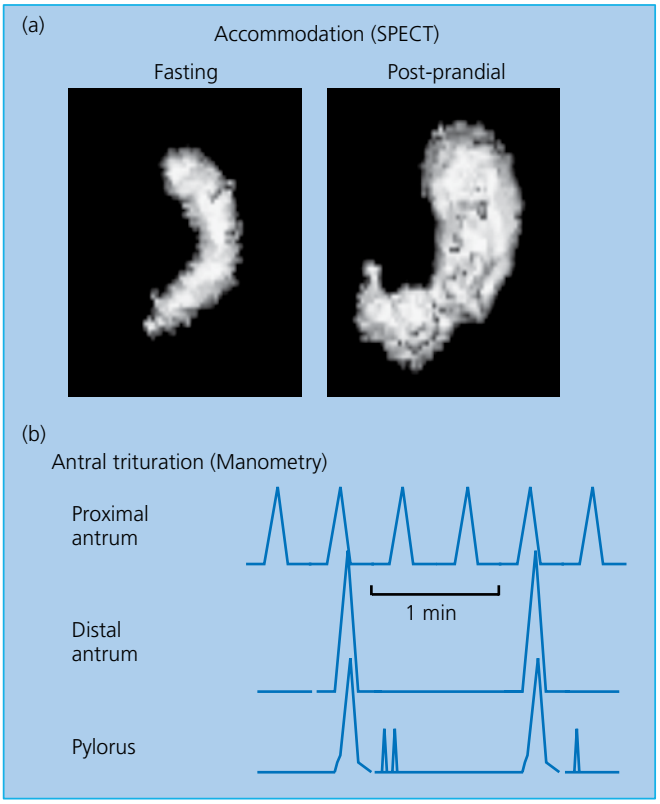

Figure 55.2 Assessment of gastric motor functions. (a) Gastric accommodation can be assessed by measuring the post-prandial change in gastric volume using single photoemission computed tomography (SPECT). The stomach wall is labelled with intravenous [^{99m}Tc]pertechnetate. Food is subsequently transferred to the antrum. (b) Manometry demonstrates that the distal antrum and pylorus contract synchronously to grind food into smaller particles. Only particles 2 mm or smaller can be emptied through the pylorus.

intestine, colonic transit is relatively prolonged, permitting digestion (i.e. of fibre) and absorption (i.e. of water and electrolytes) to be completed.

Pathophysiology of diabetes-related enteropathy: insights from animal studies

In animal models, extrinsic neural dysfunction has been primarily ascribed to a loss of myelinated and unmyelinated fibres, without much neuronal loss [28, 29]. The loss of nerve fibres is often multifocal, suggestive of ischaemic injury. Within the enteric nervous system, reduced neuronal staining and, to a lesser extent, neuronal loss, particularly inhibitory neurons expressing nitric oxide synthase (NOS), have been described in several animal models of diabetes [23]. In theory, this reduction in nitrergic inhibitory functions may contribute to impaired gastric accommodation and accelerated intestinal transit in diabetes. Reduced sympathetic inhibition may also contribute to accelerated intestinal transit. Since nitric oxide (NO) is a mediator of pyloric relaxation, loss of NOS may impair pyloric relaxation and thereby retard gastric emptying. Loss of ICC, documented in several animal models and case reports of diabetes, may also contribute to gut dysmotility [22, 30]. In addition, loss of ICC and increase in CD45 and CD68 immunoreactivity are the commonest enteric neuropathological abnormalities in diabetic and idiopathic gastroparesis [31, 32].

Several mechanisms, including apoptosis, oxidative stress, advanced glycation end-products, and neuroimmune mechanisms, may be responsible for neuronal loss and gut dysmotility [23]. The loss of ICC has been attributed to a reduction in haem-oxygenase (HO-1) and other protective mechanisms against hyperglycaemia [22]. The effects of diabetes on neuronal morphology and functions are reversible. Insulin or pancreas transplantation improved glycaemia and the axonopathy affecting autonomic nerves in rats with diabetic autonomic neuropathy [33]. Insulin also restored expression of NOS and gastric emptying in animal

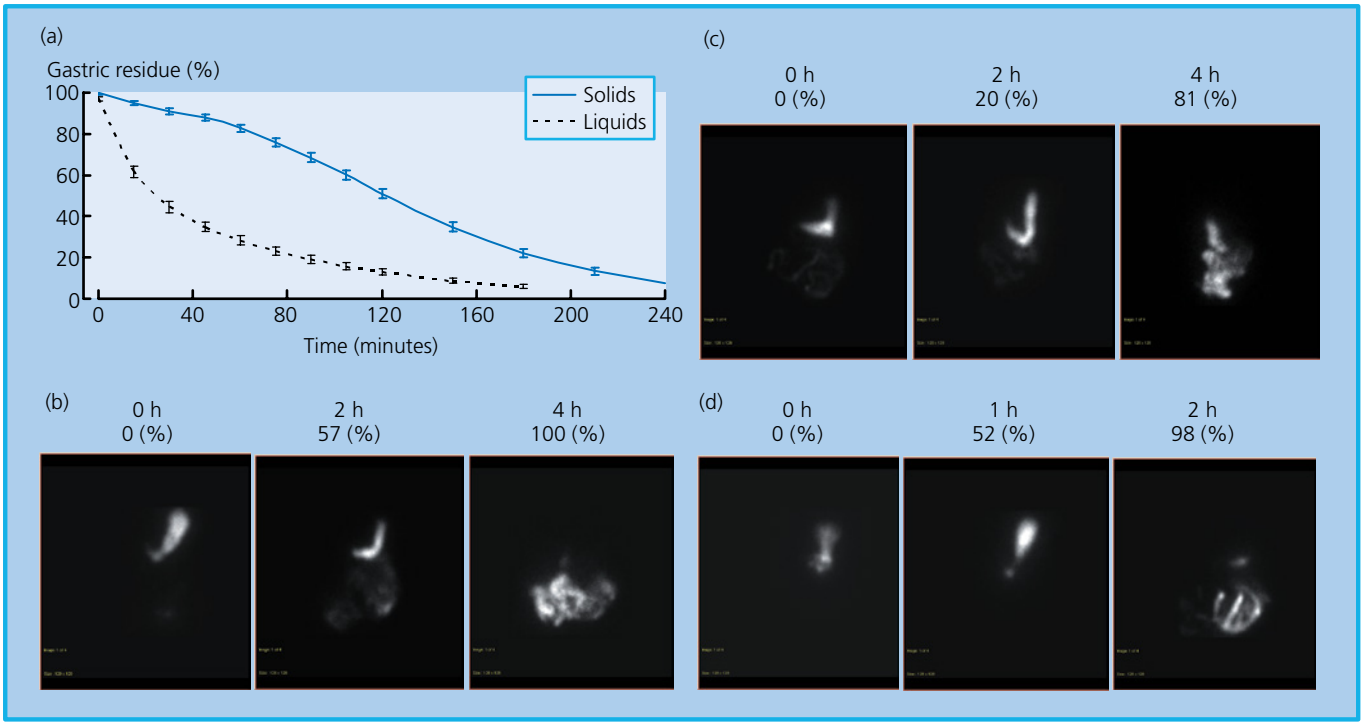

Figure 55.3 Assessment of gastric emptying by scintigraphy. Normally liquids are emptied in a linear manner, whereas solid emptying has an exponential profile, characterized by an initial lag phase, followed by a more rapid, linear emptying (a). The lag phase corresponds to the time required for antral trituration and gastric accommodation, during which ~10% of solids are emptied (b–d). Representative examples of normal, delayed, and accelerated gastric emptying, respectively, of an egg meal, labelled with ^{99m}Tc, in people with diabetes. At time 0 (i.e. the first image in each panel), the entire meal was in the stomach. Thereafter, the normal ranges for gastric emptying are 11–39% at 1 h, 40–76% at 2 h, and 84–98% at 4 h.

models of diabetes, and insulin and insulin-like growth factors prevented the loss of ICC in cultures [34, 35]. Since ICC do not express receptors for either hormone, these effects are perhaps mediated by smooth-muscle secretion of stem cell factor, which is the most important growth factor for ICC, rather than directly by insulin and insulin-like growth factors [22]. Overexpression of glial cell line–derived neurotrophic factor, a trophic factor for enteric neurons, in transgenic mice reversed hyperglycaemia-induced apoptosis of enteric neurons and improved gastric emptying and intestinal transit [36]. The effects of hyperglycaemia on enteric neurons (apoptosis) appear to be counterbalanced by the positive effects on ICC (increased kit expression) and cholinergic responses, as observed in obese, leptin receptor knockout mice [37]. Therefore, the overall effects of hyperglycaemia are unclear from a mechanistic perspective.

Modulation of M2 macrophages and oxidative stress in gastroparesis

Macrophage-based immune dysregulation is associated with delayed gastric emptying in diabetic mice [38]. The biochemical mechanism leading to loss of these different pacemaker cells is considered to be oxidative stress, and the depletion of anti-inflammatory resident M2 macrophages expressing HO-1 is believed to be the underlying pathobiology. Loss of anti-inflammatory macrophages and increased expression of genes associated with pro-inflammatory macrophages have been reported in full-thickness gastric biopsies from people with gastroparesis. It has also been demonstrated that abnormalities in the enteric neural control, including disorders of different pacemaker cells (ICC and platelet-derived growth factor receptor α [PDGFRα] fibroblast-like cells) and alterations in numbers of nitrergic neurons and CD206-positive macrophages, are associated with idiopathic or diabetic gastroparesis manifesting as delayed gastric emptying [31, 32].

Based on transcriptomic studies of full-thickness gastric body biopsies from people with gastroparesis and deep RNA sequencing and reverse transcription polymerase chain reaction (RT-PCR), many differentially expressed genes involved in immune functions such as cytokines and interleukins were actually downregulated, and there were no significant differences in enrichment of genes associated with M1 or M2 macrophages in the diabetic gastroparesis and diabetic control samples [39, 40].

In addition, proteomic studies [41] of full-thickness gastric antrum biopsies obtained from 9 people with diabetic gastroparesis and 5 individuals without diabetes revealed the following proteins to be underexpressed: trefoil factor 2 (TFF2), fatty acid-binding protein (FABP3 heart), glycerol-3-phosphate dehydrogenase (GPD1 [NAD(+)]), trypsin-1 (PRSS1), interleukin-1 receptor type 2 (IL-1R2), granulocyte colony-stimulating factor 3 (CSF3), carbonic anhydrase 3 (CA3), and α-2-HS-glycoprotein (AHSG), as well as carbonic anhydrase 1 (CA1). The only protein overexpressed was calcium/calmodulin-dependent protein kinase type II subunit-β (CAMK2B). These proteins are involved predominantly in tissue repair, cellular metabolism, or translation of ligand-receptor interaction to cellular function. Thus, other than responses to the cytokine interleukin-1 (IL-1/IL-1R2) and IL-6 (CSF3), which are downregulated, there do not appear to be consistent immune- or inflammation-related

abnormalities in proteins expressed in the antrum, which is the locus of significantly reduced function (antral hypomotility) in diabetic gastroparesis.

Pathophysiology of diabetes-related enteropathy in humans

Gastric dysfunction

In over 100 individuals who underwent gastric motor function tests to investigate the cause of upper gastrointestinal symptoms, approximately a quarter of the individuals had either abnormal gastric emptying, reduced gastric accommodation, abnormalities in both emptying and accommodation, or normal motor functions [42].

After initial evidence suggesting that there was no significant relationship of abnormal gastric emptying and symptoms and responses to prokinetics, two systematic reviews and meta-analyses have reported that when measured optimally (≥3 h, solid-phase meal), delayed gastric emptying was significantly associated with symptoms (early satiety and fullness) [42], and improvement in gastric emptying was associated with significant improvement in symptoms [43].

Neuropathy

Diabetes is associated with accelerated or delayed gastric emptying, increased and reduced gastric sensation, and impaired gastric accommodation (Figure 55.4) [45]. A vagal neuropathy can cause antral hypomotility and/or pylorospasm, which may delay gastric emptying [46]. The pathophysiology of rapid gastric emptying in diabetes is less well understood. Conceivably, impaired gastric accommodation resulting from a vagal neuropathy [47] may increase gastric pressure and thereby accelerate gastric emptying of liquids. However, the relationship between rapid gastric emptying and impaired gastric accommodation has not been substantiated. The relationship between vagal neuropathy and impaired postprandial accommodation is unclear, since accommodation may be preserved even in persons with diabetes with vagal neuropathy [48]; this may reflect non-vagal adaptive mechanisms involving enteric neurons [49]. Some people with diabetes and gastroparesis also have small intestinal dysmotility, more frequently characterized by reduced than by increased motility [50]. Small bowel dysmotility may also contribute to gastric stasis.

Hyperglycaemia

Acute hyperglycaemia delays gastric emptying in healthy individuals and in people with type 1 diabetes [51–55]. These effects may be explained by hyperglycaemia-induced suppression of antral motility and migrating motor activity (i.e. the intestinal 'housekeeper') [56–58]. However, the effects of acute hyperglycaemia on gastric emptying are modest. Indeed, even in type 1 diabetes, severe acute hyperglycaemia (i.e. 16–20 vs 4–8 mmol/l) prolonged the gastric emptying half-time by only 17 minutes (i.e. from 124 to 141 minutes). Acute modulation of blood glucose within the physiological post-prandial range (4–8 mmol/l) can also delay gastric emptying to a lesser extent [54]. Cross-sectional studies suggest that higher glycated haemoglobin (HbA_{1c}) concentrations are associated with a higher prevalence of gastrointestinal symptoms and slower gastric emptying among people with diabetes in the community [6, 59]. Although strict glycaemic management improves neural, renal, and retinal functions in diabetes, the impact on gastric emptying is unclear [60]. Improved glycaemic levels did not improve gastric emptying one week later in 10 people with type 2 diabetes [61]. Likewise, overnight and sustained (six months) improvements in glycaemic levels did not affect gastric emptying in 30 individuals with suboptimally managed diabetes [62]. In addition to hyperglycaemia, electrolyte imbalances due to diabetic ketoacidosis (e.g. hypokalaemia) and uraemia may also aggravate impaired motor function in persons with diabetes.

Recent studies have formally appraised the contribution of hyperglycaemia to impaired gastric emptying. Although acute, severe, and chronic hyperglycaemia can delay gastric emptying, there is limited evidence that delayed gastric emptying is an independent risk factor for elevated HbA_{1c} or hypoglycaemia in

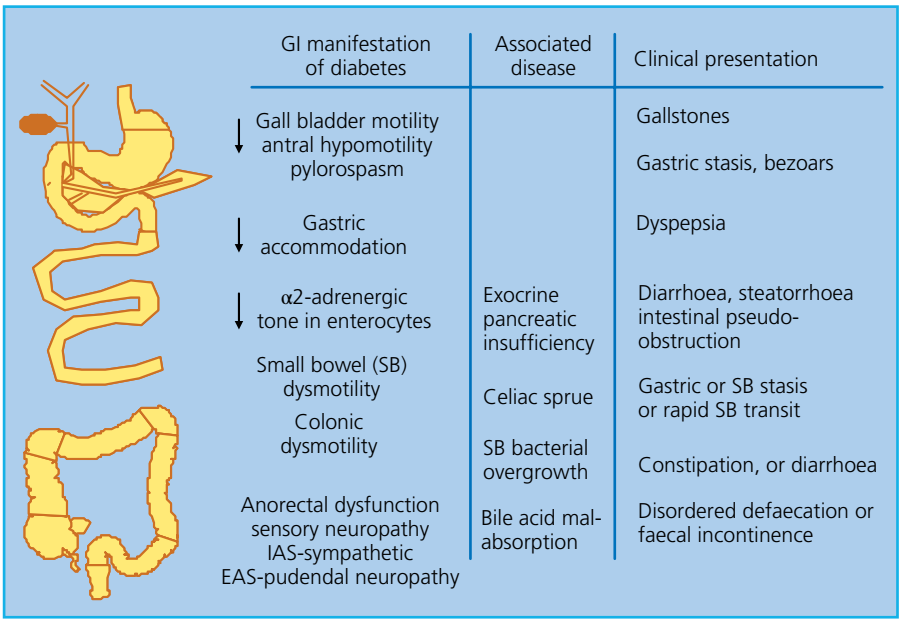

Figure 55.4 Pathophysiology of diabetes enteropathy in humans. GI, gastrointestinal; IAS, internal anal sphincter; EAS, external anal sphincter. Source: Adapted by permission from Camilleri 1996 [44].

diabetes, based on a systematic review of the literature [55]. Among 78 participants with type 1 diabetes followed for 20 years in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, delayed gastric emptying was associated with early and long-term hyperglycaemia (i.e. the HbA_{1c} at entry into the Diabetes Control and Complications Trial (DCCT) approximately 27 years previously, the duration of diabetes before DCCT entry, and mean HbA_{1c} over 27 years during DCCT-EDIC) [63].

Iatrogenic gastroparesis: opioids and glucagon-like peptide 1 receptor agonists

A confounding factor to the diagnosis of diabetic gastroparesis is the increased use of opioid medications for abdominal pain [64]. Among 583 individuals in the NIH Gastroparesis Consortium database, 41% were taking opioids, which included 33% on potent morphine-like agents. Moreover, the indication for the opioid was abdominal pain for 61% of the individuals. These persons also had higher symptom scores, greater levels of gastric retention, worse quality of life, increased hospitalization, and increased use of antiemetic and pain modulator medications compared with non-users or those using weaker opioids (e.g. tramadol, tapentadol, codeine, or propoxyphene) [65]. It has been proposed that such individuals receive a therapeutic trial with a peripherally active mu-opioid receptor antagonist to differentiate the relative contributions of the opioid and underlying disease to the gastroparesis [7, 64]. Opioids induce multiple actions that lead to gastric emptying delay or gastroparesis, including antral hypomotility and pylorospasm [66].

Iatrogenic gastroparesis may result from treatment with amylin analogues such as pramlintide [67] or glucagon-like peptide 1 (GLP-1) receptor agonists such as liraglutide and exenatide. Effects of the latter have been documented in the literature in the gastric emptying of liquids [68, 69], with clinically relevant delays in the gastric emptying of solids [70]. Short-acting GLP-1 receptor agonists (e.g. GLP-1, exenatide, lixisenatide) delay gastric emptying to a greater extent [71, 72] than the longer-acting agents (liraglutide, exenatide once weekly, and semaglutide) [73].

Diabetic diarrhoea

It is useful to categorize the pathophysiology of diabetic diarrhoea into conditions that are or are not associated with malabsorption (Figure 55.5). Involvement of sympathetic fibres, which normally inhibit motility and facilitate absorption via α_2-adrenergic receptors, can result in accelerated small intestinal transit and cause diarrhoea [74]. Artificial sweeteners such as sorbitol may also contribute to diarrhoea. People with rapid ileal transit may have bile acid malabsorption [75, 76], and deconjugated bile acids induce colonic secretion.

Features suggestive of malabsorption such as anaemia, macrocytosis, or steatorrhoea should prompt consideration of bacterial overgrowth, small bowel mucosal disease, or pancreatic insufficiency. Small intestinal dysmotility predisposes to bacterial overgrowth, which can cause bile salt deconjugation, fat malabsorption, and diarrhoea. Although type 1 diabetes is associated with coeliac disease, most people with coeliac disease and type 1 diabetes in the community are asymptomatic [77]. Chronic pancreatic insufficiency may result from pancreatic atrophy, disruption of cholinergic enteropancreatic reflexes, or elevated serum hormonal levels of glucagon, somatostatin, and pancreatic polypeptide, which reduce pancreatic enzyme secretion [78]. However, the association between chronic pancreatic insufficiency and diabetes is uncommon. Moreover, because there is sufficient pancreatic reserve, only 10% of pancreatic function is sufficient for normal digestion.

Faecal incontinence

Loose stools and anorectal dysfunction contribute to faecal incontinence in diabetic diarrhoea. Compared with continent persons with diabetes and people without diabetes, people with diabetes

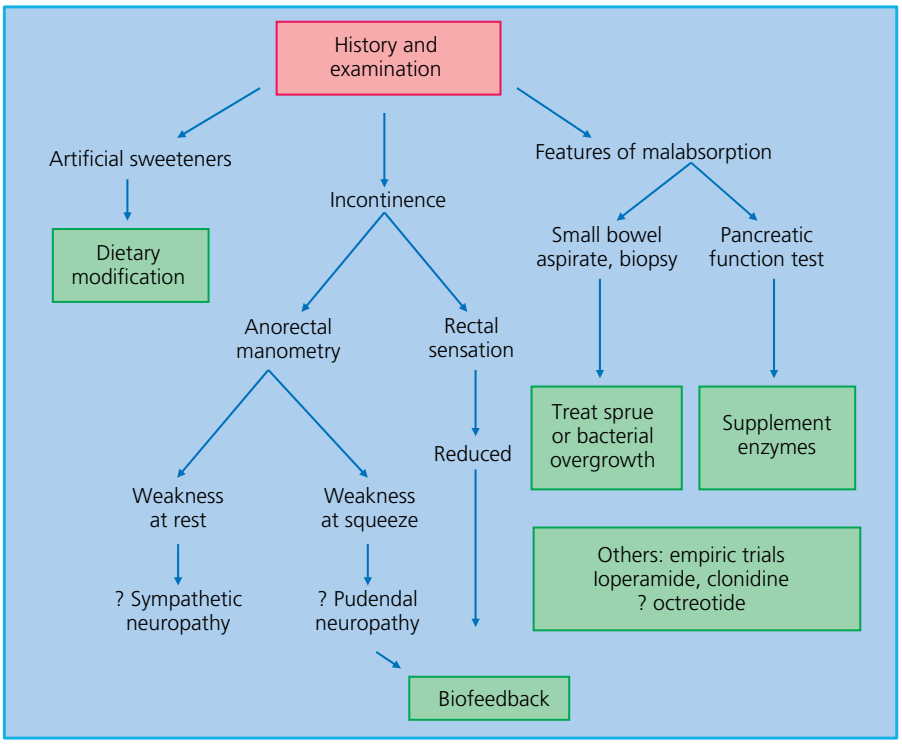

Figure 55.5 Management of diarrhoea in diabetes mellitus. Source: Adapted by permission from Camilleri 1996 [44].

and faecal incontinence have a higher threshold for rectal perception of balloon distention (i.e. reduced sensation) [79, 80]. A sympathetic neuropathy may impair internal anal sphincter function, causing reduced anal resting pressure. A pudendal neuropathy may result in reduced anal squeeze pressure.

Constipation

The mechanisms of constipation in diabetes have not been carefully studied and are poorly understood. Clinical observations suggest that, similar to idiopathic chronic constipation, both colonic dysmotility and anorectal dysfunctions (i.e. impaired anal sphincteric relaxation during defaecation) may contribute to constipation in diabetes [81]. Persons with colonic dysmotility have an impaired colonic contractile response to a meal and delayed colonic transit [82]. People with reduced rectal sensation may not perceive the desire to defaecate. Compared with euglycaemia, acute hyperglycaemia inhibited the colonic contractile response to gastric distention and proximal colonic contraction elicited by colonic distention in healthy people without diabetes [83]. However, acute hyperglycaemia did not significantly affect fasting or post-prandial colonic tone, motility, compliance, and sensation, or rectal compliance and sensation in healthy people [84].

In addition to these factors, it is also important to consider the role of psychological factors in the perception and impact of gastrointestinal symptoms. Indeed, psychosomatic symptoms are significantly associated with the reporting of gastrointestinal symptoms [4]. A systematic review of 42 studies observed that diabetes is associated with depression; the prevalence of depression among persons with diabetes (i.e. 9–27%) is approximately two-fold greater than in individuals without diabetes [85]. The severity of the depression is associated with the magnitude of hyperglycaemia in type 1 diabetes and type 2 diabetes [86] and with the prevalence of complications of diabetes (i.e. retinopathy, nephropathy, neuropathy, macrovascular complications, and sexual dysfunction) [87]. Among 200 936 persons with depression, 74 160 (36.9%) had diabetes, of whom 57 418 (28.6%) had complications [88]. Among individuals with depression, the incidence of serious psychiatric outcomes was greater in persons with (6.7%) than without diabetes (3.3%). In the National Institutes of Diabetes and Digestive and Kidney Disorders (NIDDK) Gastroparesis Consortium study, nearly 50% of the participants had clinically significant anxiety and moderate to severe depression [89]. Taken together, these findings underscore that depression is common, often severe, and may contribute to the expression of gastrointestinal sensorimotor dysfunctions in diabetes.

Several medications for the treatment of diabetes have gastrointestinal side effects: metformin can cause diarrhoea, and, among other medications, verapamil and anticholinergic agents can cause constipation.

Clinical manifestations

Dysphagia and heartburn

Oesophageal dysmotility, typically characterized by impaired peristalsis with simultaneous contractions, is common, may cause dysphagia, and may be related to cardiovascular autonomic neuropathy [90]. The amplitude of peristaltic contractions and basal lower oesophageal sphincter pressures is generally normal. Symptoms of gastroesophageal reflux are also common, particularly in persons with impaired gastric emptying who have vomiting. Rarely, recurrent vomiting may lead to Mallory–Weiss tears and bleeding.

Dysphagia and heartburn should prompt upper gastrointestinal endoscopy to exclude reflux and other incidental mucosal diseases (e.g. candidiasis, neoplasms). Although manometry may reveal oesophageal peristaltic disturbances in persons with significant dysphagia that is not explained by a structural lesion, it is unlikely to alter management, except rarely in people in whom another disorder (i.e. achalasia) is responsible for the dysphagia. Because of the high prevalence of coronary atherosclerosis in diabetes, testing for coronary artery disease should be considered when necessary in those with chest pain.

Dyspepsia and gastroparesis

Although gastroparesis refers to a syndrome characterized by symptoms (i.e. nausea, vomiting, early satiation after meals, and impaired nutrition) and objective evidence of markedly delayed gastric emptying, gastric retention may be asymptomatic [91], perhaps because of the afferent dysfunction associated with vagal denervation [92]. Nausea and vomiting typically occur in episodes lasting days to months, or in cycles. Nausea and vomiting may be associated with impaired glycaemic management and often cause hypoglycaemia, perhaps because delivery of food into the small bowel for absorption is not sufficient to match the effects of exogenous insulin.

Consistent with the concept of a paralysed stomach, the term gastroparesis should be restricted to people with markedly delayed gastric emptying. When the delay in gastric emptying is not severe, the term diabetic dyspepsia is perhaps more appropriate. Dyspepsia is characterized by one or more, generally post-prandially, upper gastrointestinal symptoms (i.e. bloating, post-prandial fullness, and upper abdominal pain). Typically, vomiting is not severe, but significant weight loss secondary to reduced caloric intake is not unusual in people with dyspepsia. In addition to delayed gastric emptying, impaired gastric accommodation and abnormal (i.e. increased or decreased) gastric sensation may also contribute to symptoms in diabetes [93, 94]. Nonetheless, the distinction of dyspepsia from gastroparesis is challenging, since there is no official distinction between moderately and severely delayed gastric emptying. Clinical experience suggests that gastric emptying of <65% at four hours reflects a significant delay, as it is often associated with nutritional consequences, thus resulting in the need for nutritional supplementation, jejunal feeding, or gastric decompression [95].

Gastric retention may be asymptomatic in some people, possibly owing to afferent dysfunction in the setting of vagal denervation, and delayed gastric emptying may be associated with recurrent hypoglycaemia in people without upper gastrointestinal symptoms.

People with diabetic gastroparesis frequently have long-standing type 1 diabetes with complications (i.e. retinopathy, nephropathy, peripheral neuropathy, and other forms of autonomic dysfunction including abnormal pupillary responses, anhidrosis, gustatory sweating, orthostatic hypotension, erectile dysfunction, retrograde ejaculation, and dysfunction of the urinary bladder) (Table 55.1). By contrast, earlier studies suggested that rapid gastric emptying of liquids is a relatively early manifestation of type 2 diabetes [96–100]. Clinicians have relied on the manifestations of complicated diabetes and on certain symptoms (e.g. vomiting of undigested food eaten several hours previously and weight loss) and signs (e.g. a gastric succussion splash or features of an autonomic neuropathy) to predict delayed gastric emptying in people with diabetes who present with upper gastrointestinal symptoms. However, several

studies have shown that symptoms are of limited utility for predicting delayed gastric emptying in diabetes [101–107]. Similarly, the type and duration of diabetes, HbA_{1c} levels, and extraintestinal complications were, in general, not useful for discriminating normal from delayed or rapid gastric emptying. However, significant weight loss and a neuropathy were risk factors for delayed and rapid gastric emptying, respectively [108]. In summary, upper gastrointestinal symptoms in persons with diabetes may result from accelerated gastric emptying, often in association with vagal neuropathy and impaired proximal gastric accommodation. Hence, it is essential to measure gastric emptying in people with upper gastrointestinal symptoms.

People with diabetic gastroparesis may have other features caused by autonomic neuropathy. Table 55.2 provides a summary of commonly performed autonomic tests.

In people with upper gastrointestinal symptoms, an upper endoscopy is necessary to exclude peptic ulcer disease and neoplasms, either of which can cause gastric outlet obstruction. Upper endoscopy may reveal gastric bezoars, which suggest antral hypomotility. Metabolic derangements, such as diabetic ketoacidosis or uraemia, and medications, particularly opiates, calcium channel blockers, and anticholinergic agents, may contribute to dysmotility. Rarely, people with gastroparesis present with retrosternal or epigastric pain, and cardiac, biliary, or pancreatic disease may be considered. Recent data also show that upper gastrointestinal symptoms may be associated with impairment of gastric accommodation [41]; this can be measured radiologically using single

Table 55.1 Symptoms and signs of autonomic dysfunction.

Sympathetic	Parasympathetic
Failure of pupils to dilate in the dark	Fixed, dilated pupils
Fainting, orthostatic dizziness	Lack of pupillary accommodation
Constant heart rate with orthostatic hypotension	Sweating during mastication of certain foods
Absent piloerection	Decreased gut motility
Absent sweating	Dry eyes and mouth
Impaired ejaculation	Dry vagina
Paralysis of dartos muscle	Impaired erection
	Difficulty with emptying urinary bladder
	Recurrent urinary tract infections

Table 55.2 Commonly performed autonomic tests.

Test	Physiological functions tested	Rationale	Comments/pitfalls
Sympathetic function			
Thermoregulatory sweat test (% surface area of anhidrosis)	Preganglionic and postganglionic cholinergic	Stimulation of hypothalamic temperature Control centres	Cumbersome, whole-body test
Quantitative sudomotor axon reflex test (sweat output, latency)	Postganglionic cholinergic	Antidromic stimulation of peripheral fibre by axonal reflex	Needs specialized facilities
Heart rate and blood pressure responses			
Orthostatic tilt test	Adrenergic	Baroreceptor reflex	Impaired responses if intravascular volume is reduced
Postural adjustment ratio	Adrenergic	Baroreceptor reflex	Impaired responses if intravascular volume is reduced
Cold pressor test	Adrenergic	Baroreceptor reflex	Impaired responses if intravascular volume is reduced
Sustained hand grip	Adrenergic	Baroreceptor reflex	Impaired responses if intravascular volume is reduced
Plasma norepinephrine response to			
Postural changes	Postganglionic adrenergic	Baroreceptor stimulation	Moderate sensitivity, impaired response if intravascular volume is reduced
Intravenous edrophonium	Postganglionic adrenergic	Anticholinesterase 'stimulates' postganglionic fibre at prevertebral ganglia	False negatives caused by contributions to plasma norepinephrine from many organs
Parasympathetic function			
Heart rate (RR) variation with deep breathing	Parasympathetic	Vagal afferents stimulated by lung stretch	Best cardiovagal test available, but not a test of abdominal vagus
Supine/erect heart rate	Parasympathetic	Vagal stimulation by change in central blood volume	Cardiovagal test
Valsalva ratio (heart rate, max/min)	Parasympathetic	Vagal stimulation by change in central blood volume	Cardiovagal test
Gastric acid secretory or plasma pancreatic polypeptide response to modified sham feeding or hypoglycaemia	Parasympathetic	Stimulation of vagal nuclei by sham feeding or hypoglycaemia	Abdominal vagal test, critically dependent on avoidance of swallowing food during test
Nocturnal penile tumescence	Pelvic parasympathetic7	Integrity of S2–4	Plethysmographic technique requiring special facilities
Cystometrographic response to bethanechol	Pelvic parasympathetic	Increase in intravesical pressure suggests denervation supersensitivity	Tests parasympathetic supply to bladder, not bowel

Source: Reproduced by permission from Camilleri and Ford 1994 [109]. Copyright 1994 Elsevier.

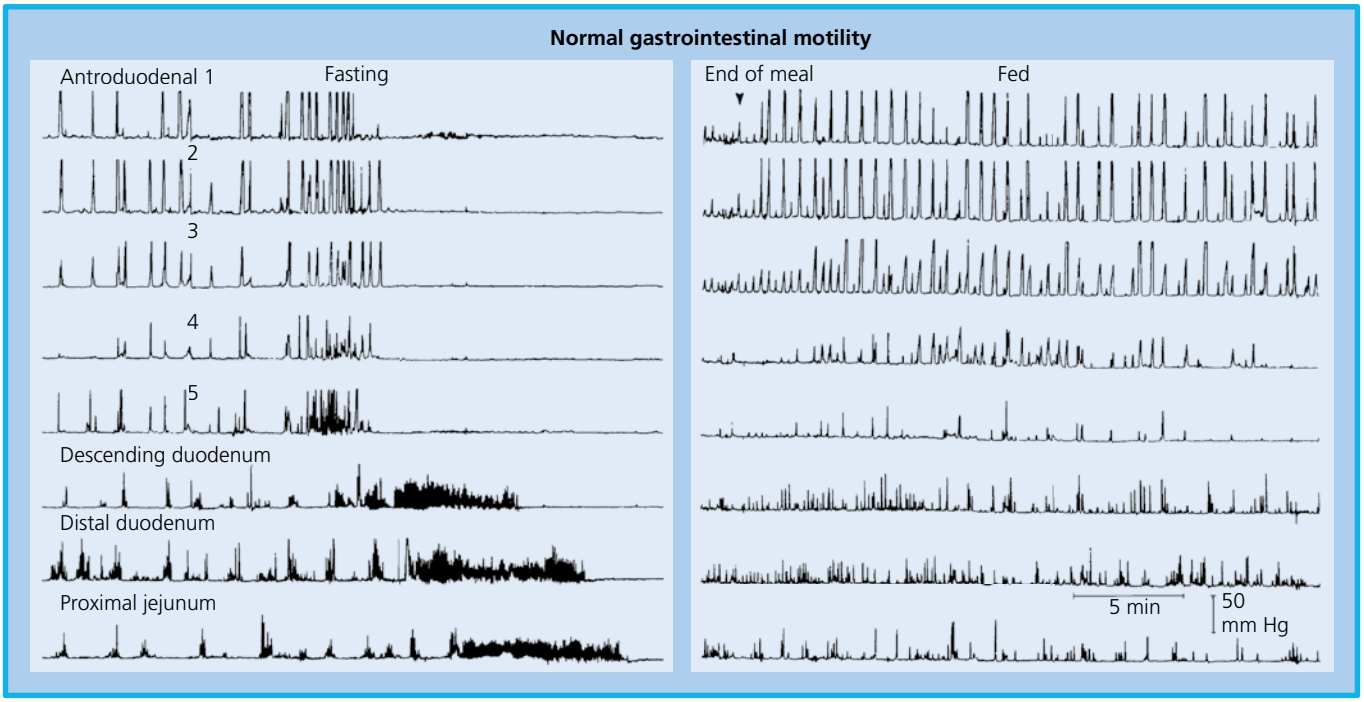

Figure 55.6 Normal manometric profile (fasting and post-prandial). The migrating motor complex characteristic of the fasting state is demonstrated by the presence of quiescence (phase I), intermittent activity (phase II), and an activity front (phase III). The post-prandial profile shows high-amplitude, irregular, but persistent phasic pressure activity at all levels. Source: Reproduced by permission from Malagelada et al. 1986 [114].

photoemission computed tomography (SPECT) or magnetic resonance imaging (MRI). Simpler approaches more widely available are a nutrient drink test (in which the maximum tolerated caloric load of less than 750 kcal would suggest impaired accommodation [110] and 206 kcal is diagnostic of impaired accommodation [111]), or a water load test where a volume ingested over five minutes is measured [111].

Barium X-rays of the small intestine or enterography with computed tomography should be considered only when the clinical features raise the possibility of small intestinal obstruction. Gastric emptying of solids should be quantified by scintigraphy or stable isotope breath test [112, 113], and antroduodenal manometry may be considered in selected circumstances. Measurements of pressure profiles in the stomach and small bowel can confirm motor disturbances and may facilitate the selection of patients for enteral feeding (Figure 55.6). People with gastroparesis due to predominant antral hypomotility as a result of diabetic enteropathy may tolerate feeding delivered directly into the small bowel, whereas those with a more generalized motility disorder may not.

Diarrhoea and constipation

The term *diabetic diarrhoea* was first coined in 1936 by Bargen at the Mayo Clinic to describe unexplained diarrhoea associated with severe diabetes [115]. Diabetic diarrhoea is typically chronic, may be episodic, and can be severe. Diarrhoea can occur at any time, but is often nocturnal and may be associated with anal incontinence, which may indicate internal anal sphincter dysfunction. Persons with diarrhoea commonly have symptoms of delayed gastric emptying such as early satiety, nausea, and vomiting.

Constipation may occur in isolation or alternate with episodes of diarrhoea. Many physicians regard constipation to be synonymous with infrequent bowel movements. It is important to characterize symptoms because many people have misconceptions about normal bowel habits. For example, it is not necessary to have a bowel movement daily – the normal range varies from three bowel movements every week to every day. Moreover, by constipation, people refer to one or more of a variety of symptoms (i.e. infrequent stools, hard stools, excessive straining during defaecation, a sense of anorectal blockage during defaecation, the need for anal digitation during defaecation, and a sense of incomplete evacuation after defaecation) [116]. Some of these symptoms (e.g. a sense of anorectal blockage during defaecation) may suggest disordered evacuation. A careful rectal examination during relaxation and straining is needed to exclude rectal mucosal lesions and to detect the presence of rectal prolapse, rectocele, and disordered defaecation. Normally, voluntary contraction is accompanied by upward and anterior motion of the palpating finger towards the umbilicus as the puborectalis contracts. Conversely, the puborectalis should relax and the perineum should descend (by 2–4 cm) during simulated evacuation. The rectal examination may suggest features (i.e. reduced or increased perineal descent, paradoxical contraction of puborectalis) of defaecatory disorders.

Abdominal pain

People with diabetes are obviously susceptible to the usual causes of abdominal pain seen in the general population. There is an increased prevalence of gallstones because of altered gallbladder contractility and of mesenteric ischaemia caused by generalized atherosclerosis. However, there is little evidence that altered gallbladder contractility *per se* (i.e. in the absence of gallstones) causes symptoms. Thoracolumbar radiculopathy may result in pain in a girdle-like distribution that does not cross the midline. Specific tests are indicated if the clinical features of pain suggest these disorders. It is essential to elicit a careful history.

Diagnostic tests

Suspected gastric dysfunction

Typically, diagnostic testing is primarily guided by symptom pattern and severity. However, since persons with delayed gastric emptying are often asymptomatic, gastric emptying assessments should also be considered in those with unexplained hypoglycaemia. After initial testing to identify disturbances of transit, more detailed testing with intraluminal techniques (i.e. manometry and/or a barostat) may be useful for characterizing motor dysfunction and guiding therapy. Delayed gastric emptying can be documented by scintigraphy, stable isotope breath test, or the presence of a large amount of retained food in the stomach. Barium studies and scintigraphy using labelled liquid meals are of limited value for identifying dysmotility because the gastric emptying of liquids and semi-solids (e.g. mashed potatoes) frequently is normal, even in the presence of moderately severe symptoms. The tests that are available to measure gastric emptying non-invasively are summarized in Table 55.3.

Assessment of solid emptying by means of a radiolabel that tags the solid phase of the meal is a more sensitive test with a well-defined normal range. The proportion of radioisotope retained in the stomach at two and four hours distinguishes normal function from delayed gastric emptying with a sensitivity of 90% and a specificity of 70% [118]. The importance of obtaining scans for four hours after a meal cannot be overemphasized. Since gastric emptying is slow initially, it is not accurate to extrapolate emptying from scans taken for a shorter duration. Another useful test for measuring solid-phase gastric emptying utilizes a standardized meal with a biscuit enriched with ^{13}C, a substrate containing the stable isotope. When metabolized, the proteins, carbohydrates, and lipids of the *Spirulina platensis* or the medium-chain triglyceride, octanoate, give rise to respiratory CO_2 that is enriched in ^{13}C. Measurement of $^{13}CO_2$ breath content (a reflection of the amount of biscuit remaining in the stomach) by isotope ratio mass spectrometry allows the estimation of gastric emptying half-life [112, 113].

The wireless motility capsule using the SmartPill™ (Medtronic, Minneapolis, MN, USA) has been approved by the US Food and Drug Administration (FDA) for the evaluation of gastric emptying and colonic transit time in people with suspected slow transit constipation, and for the measurement of pH, temperature, and pressure throughout the gastrointestinal tract [119]. It is a safe and practical alternative to gastric electrical stimulation [120]. Sensed data are transmitted by the single-use capsule to a receiver worn by the patient, and pH values from 0.5 to 9.0, pressure activity, and temperature are recorded. Gastric emptying time is defined as the time from capsule ingestion to a rise in pH from gastric baseline to >4.0, marking the passage of the capsule from the antrum to the duodenum. Normal emptying of the capsule should occur within five hours of ingestion. If it does not occur within six hours, a maximum gastric emptying time value of six hours is assigned [119]. The gastric emptying results with the wireless motility capsule are not as accurate as those using scintigraphy with a digestible solid meal. However, its advantages include point-of-care use in ambulatory settings and avoidance of the pitfalls of gastric electrical stimulation, such as radiation exposure, need for a gamma camera, and lack of standardized practices across centres [119]. The utility of the wireless motility capsule testing has been enhanced with data showing that pressure profile measurements recorded by the capsule can differentiate persons with diabetic gastroparesis from healthy individuals by the significantly lower numbers of contractions and motility indices [121].

Healthy individuals and (more likely) persons with gastroparesis may not have a phase III migrating motor complex contraction within six hours, when the next meal is given, and capsule emptying may be inhibited by the suspension of the migrating motor complex by the meal. Other limitations include possible difficulty with capsule ingestion and the potential for capsule retention or obstruction. Use of the capsule is contraindicated in children and those with a known history of oesophageal stricture.

For people with severe upper gastrointestinal symptoms, antropyloroduodenal manometry is a specialized technique that assesses pressure profiles in the stomach and small bowel and also guides management. Manometry may also reveal hypomotility of the gastric antrum and/or an intestinal neuropathy (Figures 55.6 and 55.7). Individuals with selective or dominant abnormalities of gastric function may be able to tolerate enteral feeding (delivered directly into the small bowel), unlike those with a more generalized motility disorder. Manometry may also reveal excessive tonic and phasic pressure activity at the pylorus [123]. Pyloric dysfunction is documented with a functional luminal imaging probe performed during endoscopy,

Table 55.3 Non-invasive measurements of gastric emptying.

Feature	Gastric emptying by scintigraphy	Stable isotope breath test	Wireless pressure and pH capsule
Indication/function measured	Gastric emptying	Gastric emptying	Emptying and pressure amplitude
Device, assembly or special requirements	External gamma camera and isotope-labelled meal	Breath collection vials and stable isotope-labelled meal	Intraluminal capsule with miniaturised strain gauge and pH measurement
Placement of device	–	–	Capsule swallowed
Performance/versatility/interpretation	Excellent, standardized meals, data acquisition and interpretation	Becoming standardized Performance related to mathematical analysis	Standard acquisition, delayed emptying fairly valid; pressures of unclear significance
Duration of study	Typically 4 h, could be added to small bowel and colon transit	3–4 h	6 h, could be added to small bowel and colon transit
Availability/potential use	+	+++	+
Costs	++	+	++

The '+' signs signify the lowest (+) to the highest (+++) availability or potential use.
Source: Adapted by permission from Shin and Camilleri 2013 [117]. Copyright and all rights reserved. Material from this publication has been used with the permission of the American Diabetes Association.

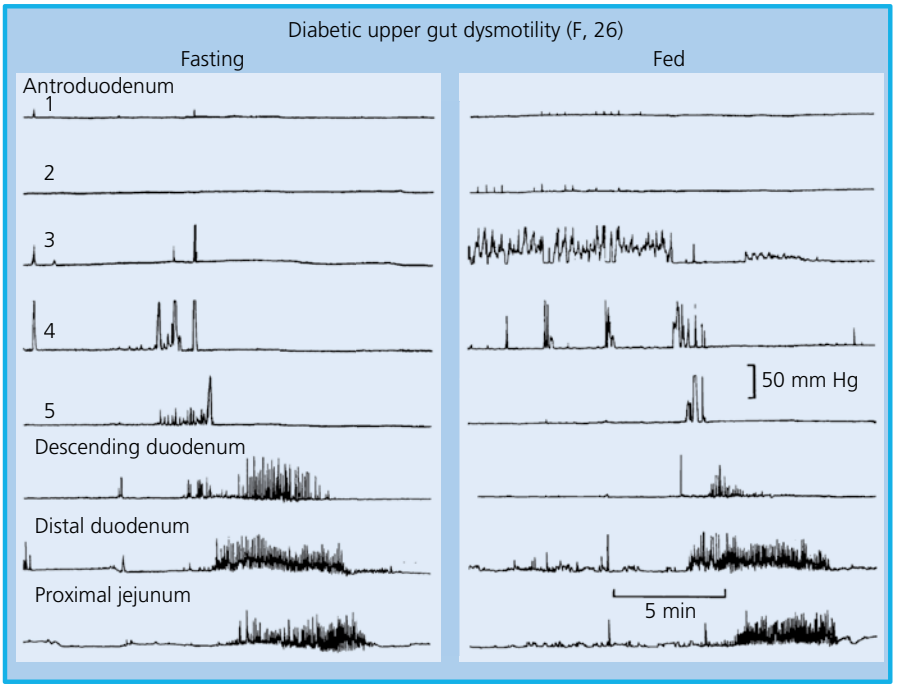

Figure 55.7 Manometric profile in a 26-year-old woman with diabetes and autonomic neuropathy, showing abnormal propagation of phase III of interdigestive motor complex and lack of a well-developed antral component in fasting tracing. Post-prandially, note antral hypomotility, pylorospasm, and failure of a meal to induce a fed pattern. Source: Reproduced by permission from Colemont and Camilleri 1989 [122].

which assesses diameter, distensibility, and compliance of the pylorus [124]. It has been proposed that this measurement might facilitate selection of those for pyloric interventions for gastroparesis.

Gastric accommodation in response to meal ingestion may be impaired in diabetes [41, 125]. This may contribute to the gastrointestinal symptoms of nausea, bloating, and early satiety. Imaging of the stomach wall using ^{99m}Tc-pertechnetate allows measurement of gastric volume after meal ingestion.

Investigation of constipation

For persons with constipation, tests of colonic transit, anorectal manometry, and rectal balloon expulsion provide a useful start to investigation. Anorectal manometry and the rectal balloon expulsion test generally suffice to diagnose or exclude defaecation disorders; MRI or barium proctography is required only in selected cases. Colonic transit is often delayed in people with defaecatory disorders. Therefore, in those with slow colonic transit, slow transit constipation can only be diagnosed after excluding defaecatory disorders. Intraluminal assessments of colonic phasic motility (by manometry) and tone (by barostat) often reveal other dysfunctions (e.g. impaired contractile responses to a meal) and/or pharmacological stimuli (e.g. bisacodyl or neostigmine) in persons with slow-transit constipation. Colonic transit can be characterized by radiopaque markers, which, depending on the technique, take 5–7 days, or by scintigraphy, which takes 24–48 hours. Both techniques are equally accurate for identifying slow or rapid colonic transit.

Small intestinal dysmotility may manifest as one or more of the following features: abnormal migrating motor complexes, failure to convert from fasting to post-prandial motor pattern, and/or features of a vagal neuropathy (i.e. excessive number of fasting migrating motor complexes or persistent post-prandial migrating motor complexes). Assessment of stool fat provides a useful differentiation point for diabetic diarrhoea, as it indicates malabsorption as the pathophysiology leading to diarrhoea. An upper endoscopy provides an opportunity to obtain duodenal aspirates for bacterial overgrowth and small bowel biopsy to exclude coeliac disease. Lactose or glucose hydrogen breath tests rely on substrate metabolism by bacterial overgrowth in the small intestine, with hydrogen release in breath excretion. However, studies have shown that the early peak is frequently due to rapid delivery of the substrate to the colon, with bacterial metabolism by normal colonic flora rather than small bowel bacterial overgrowth [126]. To reduce the potential impact of this confounding factor (i.e. rapid intestinal transit), a more restricted definition to diagnose small intestinal overgrowth may be preferable; that is, an early hydrogen peak (20 ppm), due to small intestinal bacteria, occurring at least 15 minutes before the later prolonged peak, corresponding to the passage of the remaining lactulose into the colon. However, even with more restricted definitions, the sensitivity and specificity of the lactulose hydrogen breath test in detecting small bowel bacterial overgrowth have been reported to be only 68% and 44%, respectively, and for the glucose breath test 62% and 83%, respectively [126].

Management

The principles of management are to address fluid and nutritional requirements, improve glycaemic management, and treat symptoms [127].

Gastroparesis and dyspepsia

The first step in the management of gastroparesis is to educate the person to use a small particle diet, aided with cooking of non-digestible fibre and homogenization of solids to a small particle size [128]. Although nutritional requirements and symptoms can be addressed to a variable extent in persons with mild and compensated gastroparesis, those with severe gastroparesis often require hospitalization for one or more of the following measures: intravenous hydration and correction of metabolic derangements (ketoacidosis, uraemia, hypoglycaemia, hyperglycaemia), nasoenteric

decompression, and/or enteral nutrition to manage vomiting and nutritional requirements [95]. Parenteral nutrition may become necessary in cases of malnutrition. Bezoars may be mechanically disrupted during endoscopy, followed by gastric decompression to drain residual non-digestible particles.

Erythromycin, at a dose of 3 mg/kg body weight intravenously every eight hours, can accelerate gastric emptying [129, 130]. When oral intake is resumed, treatment with oral erythromycin, 250 mg three times a day for 1–2 weeks, is worthwhile. The prokinetic effects of erythromycin are limited by tachyphylaxis. Anecdotal findings suggest that erythromycin may be effective if courses are separated by a drug-free period, lasting for example two weeks. Hyperglycaemia interferes with the prokinetic effect of intravenous erythromycin on gastric emptying in people with and without diabetes [39]. Since both liquids and homogenized solids are more readily emptied from the stomach than solids, liquid or blended food is better tolerated. Frequent monitoring of blood glucose is essential during this phase; however, improved glycaemia did not improve gastric emptying in people with suboptimally controlled type 2 diabetes [62].

For individuals with severe gastroparesis who do not respond to the measures outlined, it may be necessary to bypass the stomach with a jejunal feeding tube. This procedure should be preceded by a trial of nasojejunal feeding for a few days, with infusion rates of at least 60 ml/h of iso-osmolar nutrient. It is preferable to place jejunal feeding tubes directly into the jejunum either by endoscopy or, if necessary, by laparoscopy or mini-laparotomy, rather than via percutaneous endoscopic gastrostomy tubes. Such tubes allow restoration of normal nutritional status, but they are not without adverse effects. There is no evidence to suggest that gastrectomy relieves symptoms or enhances quality of life. People with gastroparesis often have concomitant small intestinal denervation, which is likely to cause persistent symptoms after gastrectomy [50, 131].

If the individual remains symptomatic, other prokinetic agents may be considered as adjuncts. In the USA the only available medication is metoclopramide, a peripheral cholinergic and antidopaminergic agent. During acute administration, it initially enhances gastric emptying of liquids in diabetic gastroparesis, but its symptomatic efficacy is probably related to its central antiemetic effects. However, its long-term use is restricted by a decline in efficacy and by a troubling incidence of central nervous system side effects. Therefore, it is preferred to prescribe a dose of 10 mg three times a day, administered 30 minutes before meals, for a short duration; the higher dose is 20 mg three times a day. A systematic review of trials concluded that there was limited evidence to support the use of domperidone, which is another dopaminergic antagonist not approved for use in the USA [132]. Endoscopic injection of botulinum toxin into the pylorus was not effective in controlled studies primarily of idiopathic gastroparesis [133, 134]. The neurokinin 1 (NK1) antagonist aprepitant, 125 mg/d, improved secondary outcomes but not severity of nausea in a four-week multicentre, double-masked trial of 126 participants with nausea and vomiting (57% with delayed gastric emptying) [135]. New medications in development for diabetic gastroparesis are relamorelin [136] (a pentapeptide ghrelin agonist) and tradipitant [137] (an NK1 antagonist).

Relamorelin (RM-131) is a novel pentapeptide ghrelin receptor agonist with greater potency in increasing gastric emptying in animal pharmacology studies than other ghrelin mimetics [138]. In two randomized, double-blind, placebo-controlled, crossover studies conducted in 10 people with type 2 diabetes or type 1 diabetes and prior documentation of delayed gastric emptying, relamorelin accelerated the gastric half-emptying time of solids [139, 140]. In a phase II study of persons with type 1 diabetes, relamorelin reduced upper gastrointestinal symptoms, with the most impressive effects being observed in those with high baseline vomiting [141]. In individuals with chronic constipation, relamorelin also accelerated colonic transit [142].

Although the FDA recognizes gastric electrical stimulation as a humanitarian use device for refractory gastroparesis, its use for this indication is controversial. Although published data suggest that the device reduces vomiting frequency only when the device is on, data submitted to the FDA indicated that electrical stimulation reduced vomiting frequency to a similar extent with the device turned off or on, suggesting a placebo response [143, 144]. Moreover, the device is expensive and does not accelerate gastric emptying. Between 10% and 20% of individuals have device-related complications. Recent data from a large European multicentre study showed reduced frequency of refractory vomiting in persons with and without diabetes; however, this was not associated with acceleration of gastric emptying or improved quality of life [145].

Pyloromyotomy performed either laparoscopically or endoscopically is increasingly offered to individuals with diabetic gastroparesis as well as to persons with idiopathic or postsurgical gastroparesis. At least four systematic reviews and meta-analyses [146–149] that appraised approximately 10 open-label clinical trials have demonstrated improvement in Gastroparesis Cardinal Symptom Index as well as gastric emptying by scintigraphy in the overall appraisal of gastric per oral endoscopic myotomy (G-POEM). Nevertheless, sham controlled studies are required, and the impact on outcomes of comorbidity including vagal dysfunction, antral hypomotility, and objective evidence of pyloric dysfunction requires further elucidation [150].

Diabetic diarrhoea

Diabetic diarrhoea is treated symptomatically with loperamide, preferably administered 30 minutes before meals, in the dose range of 2–16 mg/d. Consumption of artificial sweeteners that contain the osmotically active sugar substitute sorbitol should be reduced. Second-line approaches are clonidine, 0.1 mg orally [151] or by patch, in those who do not experience significant postural hypotension. Amitriptyline, which has anticholinergic effects, may reduce intestinal cramping and transit. Octreotide (25–50 µg subcutaneously 5–10 minutes before meals) delays small intestinal transit [152] and may also reduce secretory diarrhoea associated with rapid intestinal transit [153]. Although it was suggested that octreotide reduces small bowel bacterial overgrowth in chronic intestinal pseudo-obstruction [154], the study assessed bacterial overgrowth by breath testing. Indeed, by delaying small intestinal transit, octreotide may predispose to bacterial overgrowth. Regulating stool consistency may also improve faecal continence. In addition, pelvic floor retraining with biofeedback therapy can improve rectal sensation and enhance coordination between perception of rectal distention and contraction of the external anal sphincter [80]. However, biofeedback therapy is less effective in people with markedly reduced rectal sensation. A descending colostomy may be required and may improve the quality of life in those with severe diarrhoea associated with faecal incontinence.

Constipation

For people without pelvic floor dysfunction, chronic constipation can be generally managed with pharmacological agents (i.e. osmotic and stimulant laxatives) [155]. Pelvic floor retraining by biofeedback

therapy is the cornerstone for managing defaecatory disorders; laxatives are used as an adjunct to pelvic floor retraining [156]. Fibre supplementation, either with dietary supplementation or with fibre products (e.g. psyllium, 15–18 g/d), should be considered in people with inadequate fibre intake. Of the osmotic laxatives, polyethylene glycol (up to 17 g in 225 ml of water once or twice a day) is a widely used and safe over-the-counter agent. Although lactulose is a poorly absorbed disaccharide, lactulose syrup contains small amounts of absorbable sugars and may increase hyperglycaemia. Magnesium compounds are safe, but individuals with impaired renal function may develop magnesium retention. Bisacodyl or glycerine suppositories are useful rescue agents in people who have not had a bowel movement for two days. If possible, suppositories should be administered 30 minutes after a meal to synergize pharmacological therapy with the physiological response to a meal. By activating chloride channels and inducing colonic secretion, lubiprostone accelerated colonic transit in healthy individuals and improved symptoms in functional constipation [157, 158] and diabetes and constipation [159].

The anticholinesterase pyridostigmine is efficacious in relief of constipation in individuals with diabetes and constipation, and the effect is also observed in those with autonomic neuropathy [160, 161]. Several other medications are available for the treatment of chronic constipation [162], although they have not been formally or specifically tested in persons with diabetes.

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56 Diabetes and Oral Health

Palle Holmstrup[1], Christian Damgaard[1], and Allan Flyvbjerg[2,3]

[1] Department of Odontology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[2] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[3] Steno Diabetes Center Copenhagen, Copenhagen, Denmark

Key points

- The background to the present chapter is a need to present the past decades' scientific discoveries on the relationship between diabetes and oral health.
- The aim is to emphasize the importance of good oral health, which is now to be considered part of the therapeutic modalities for prevention and treatment of diabetes.
- The chapter deals with the association of diabetes with various oral diseases, including gingivitis, periodontitis, caries, hyposalivation, candidal infection, and cancer; of these, periodontitis is the most important for daily clinical management of individuals with diabetes.

Recent decades have significantly widened the perspectives of the association of medical diseases with diseases of the oral cavity, the interaction of oral tissues with diabetes probably being best documented. Hyperglycaemia, and even slightly elevated blood glucose levels, adversely affects oral health, with manifestations including widely different diseases and conditions, which include gingivitis and periodontitis, caries, candidal infection, decreased saliva secretion, and oral cancer. Oral infections associated with local and systemic inflammatory responses, on the other hand, adversely affect blood glucose levels [1].

Gingivitis and periodontitis

Most scientific data deal with interactions of periodontal diseases and diabetes, which is probably most important, because it is bidirectional and may have serious consequences for the course of both diseases. Several reviews have focused on the bidirectional association of periodontitis with diabetes, and a recent consensus report and treatment guidelines summarize the outcome of a joint workshop on periodontal diseases and diabetes by the International Diabetes Federation (IDF) and the European Federation of Periodontology (EFP) [2].

Gingivitis

The periodontal tissues are shown in Figure 56.1. Since the surface of teeth is not constantly renewed, as occurs for other surfaces of the human organism, there is an obvious possibility for bacterial accumulation with biofilm formation (plaque) on the dental surfaces. The biofilm typically accumulates along the gingival margin and if not mechanically removed, it grows and invades the gingival crevice. In response to the biofilm formation, gingivitis is a reversible inflammation limited to the gingival soft tissue. Gingivitis affects 50–90% of the adult population [3, 4] and is characterized by common signs of inflammation in the tooth-surrounding soft tissue, including redness and oedema (Figure 56.2). Bleeding is common during oral hygiene procedures and chewing in individuals with gingitivis, but pain is uncommon, which is why the inflammatory process may run an unnoticed course. Providing there is sufficient oral hygiene with tooth brushing and interdental cleaning, the dental biofilm can be removed, and the inflammatory lesion resolved without leaving permanent damage to the tooth-supporting tissues. However, without adequate biofilm removal, the condition may progress to periodontitis.

Periodontitis

Periodontitis, which is always preceded by gingivitis, is a common multifactorial inflammatory disease initiated by the accumulation of opportunistic pathogenic bacteria in biofilms formed at the tooth surface below the gingival margin [2] (Figure 56.1). The outcome of the inflammatory process includes deepening of the gingival crevice, resulting in formation of a gingival pocket with an anaerobic environment. The associated dysbiosis of the biofilm microbiota, invading the gingival pocket, leads to a non-resolving and destructive inflammatory response [5, 6]. Population studies have revealed a prevalence of around 50% in its mildest forms in adults, rising to more than 60% in individuals aged more than 65 years [7, 8]. Radiographic bone loss and clinical registrations corresponding to periodontitis in a recent Scandinavian study have been observed in as much as 72.4%. The prevalence of periodontitis increases after 40 years of age, with severe forms occurring primarily after 60 years of age [9]. Severe periodontitis affects around 11% of the adult global population [10] and is a major cause of tooth loss,

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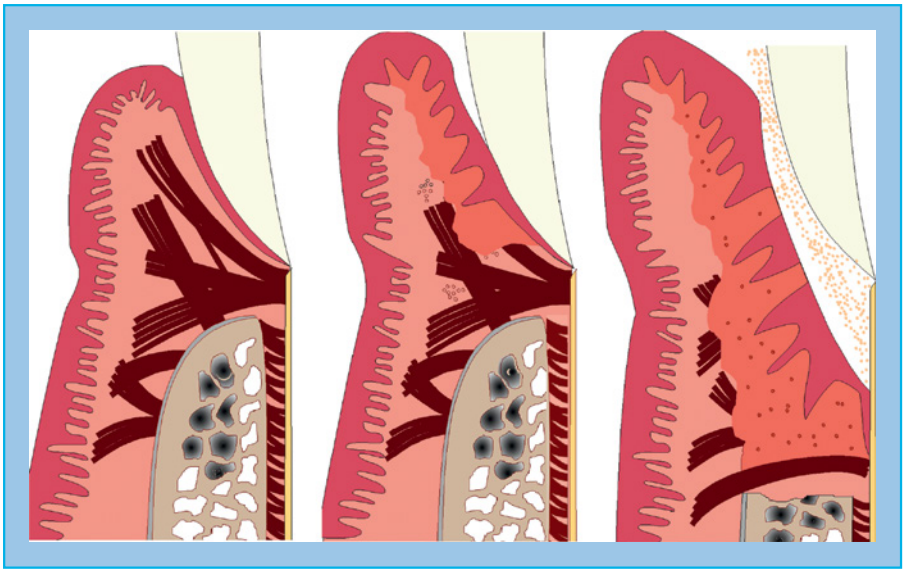

Figure 56.1 Schematic drawing of the periodontal soft and hard tissue close to the gingival margin: em, enamel; den, dentin; bone, alveolar bone; gin, gingival soft tissue with epithelial attachment to enamel in the healthy periodontum; root, root covered by cementum with periodontal ligament attaching the root to the alveolar bone. In gingivitis the gingiva is inflamed with oedema and the architecture of the epithelial attachment is changed. In periodontitis the gingival connective tissue, the periodontal ligament, and the supporting alveolar bone are undergoing degradation. There is a bacterial biofilm in the gingival pocket, and through ulcerations in the pocket epithelium bacteria have direct access to the connective tissue and the circulation. Source: © Palle Holmstrup.

Figure 56.2 Gingivitis with redness and slight swelling of marginal gingiva.

nutritional compromise, altered speech, low self-esteem, and poor quality of life [11, 12]. Periodontitis is considered the second most prevalent oral disease worldwide [13], and is the fourth most frequent illness on the Disease Global burden list [14].

The disease results in degradation of the periodontal tissues with irreversible attachment loss (Figure 56.3), including loss of alveolar bone and deepened gingival pockets with ulcerations (Figure 56.1), associated with inflammation and microbial dysbiosis. The inflammatory processes account for the tissue breakdown, which may result in gingival retraction visible as elongated teeth. As the result of alveolar bone loss (Figure 56.4) the affected teeth may loosen, change position, and ultimately, if left untreated, they may be lost (Figures 56.5 and 56.6) [15].

Determined by several factors including oral hygiene, periodontal care attendance, lifestyle, tobacco habits, medical diseases, and genetics, the individual susceptibility to periodontitis varies greatly.

(a) (b)

Figure 56.3 (a) Periodontitis with plaque covering dental calculus at the exposed root surface. Interdental papillae are lost, and the gingival margin shows irregular oedematous condition with retraction. (b) The same individual as in (a) after periodontal treatment. There is no longer inflammation, but the periodontal tissue degradation is irreversible.

(a)

(b)

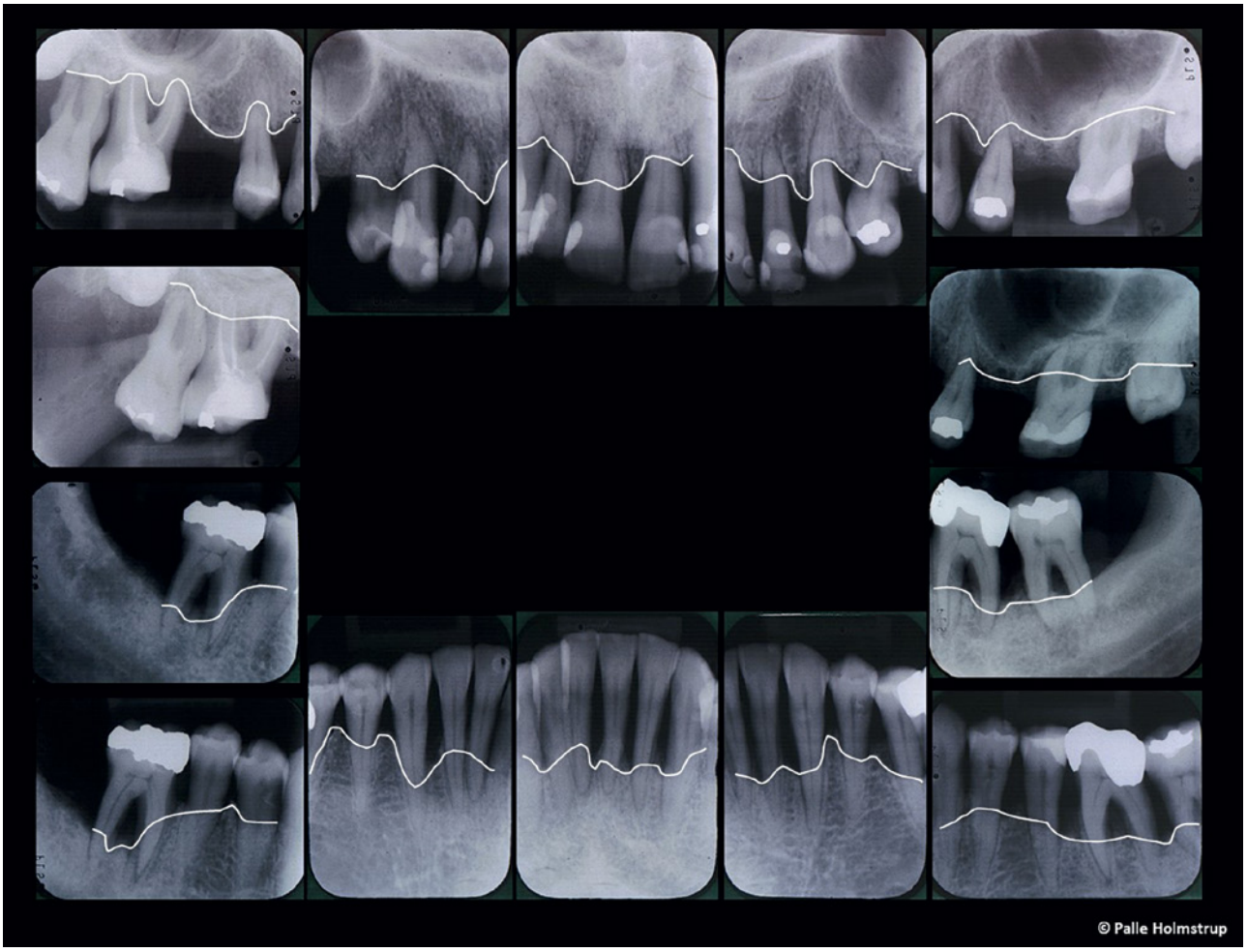

Figure 56.4 (a) A 47-year-old person with severe periodontitis causing elongated teeth due to loss of tooth-supporting tissue. (b) The same person as in (a). X-rays demonstrate major loss of alveolar bone due to severe periodontitis. Margin of bone marked with white line. While the pristine level of the bone margin is approximately 2 mm from the crown of the teeth, the supporting bone around several teeth is limited to the periapical part of the root.

It has been demonstrated in a twin study that genetics may account for as much as half of the tissue destruction [16].

An important characteristic of periodontitis is the deepened gingival pockets, the epithelial lining of which becomes ulcerated due to inflammation (Figure 56.1). Thereby bacteria from the pockets can penetrate the gingival soft tissue including the vessels, resulting in bacteraemia. This happens as a consequence of everyday procedures like chewing, tooth brushing, and flossing in individuals with periodontitis [17].

Due to its vague clinical symptoms, such as gingival oedema and bleeding, the course of periodontitis is often unnoticed by the patient until tooth loosening and changed position occur (Figure 56.5).

Figure 56.5 Severe periodontitis has caused displacement of the teeth with diastemata between upper incisors. Calculus on lower incisors.

Figure 56.6 Severe periodontitis with major loss of supporting tissue, elongated teeth, exposure of roots, and loosening. Accumulation of plaque on the root surfaces.

These are often the reason for seeking treatment. Professional root scaling with removal of biofilm and calculus is essential to stop progression of the disease. In cases with deep pockets, surgical periodontal treatment aiming at achieving improved clinical attachment levels and reducing pocket depths may be needed.

Association of diabetes with gingivitis and periodontitis

Numerous studies and reviews have described the association of diabetes with oral diseases [2, 18–21]. The incidence of gingivitis is particularly high in children and adolescents with newly discovered type 1 diabetes, and in individuals with diabetes with glycated haemoglobin (HbA_{1c}) values above 10% (86 mmol/mol) [22, 23]. Also, a higher incidence of plaque and gingivitis has been found in adolescents with both well- and dysregulated type 1 diabetes than in adolescents without diabetes [24]. In addition, children with type 1 diabetes and type 2 diabetes, respectively, generally have an increased gingival bleeding tendency through puberty, after which it appears to decrease [25].

Several cross-sectional and longitudinal studies have demonstrated that both individuals with type 1 diabetes and those with type 2 diabetes have an increased risk and severity of periodontitis compared to individuals without diabetes, and periodontitis is often mentioned as the sixth complication of diabetes [20, 26–39]. The overall risk of periodontitis in persons with diabetes has been estimated to increase by a factor of 2–3 [26]. An additional important characteristic of periodontitis in individuals with diabetes is a poorer outcome of periodontal therapy [27].

In type 1 diabetes, increased incidence and severity of periodontitis are associated with elevated HbA_{1c}, but in addition age (>32 years), duration of diabetes (>10–24 years), tobacco smoking, presence of late diabetes-related complications, and dental care habits seem to be important to the development and progression of periodontitis [22, 28].

The level of metabolic control determines the susceptibility to progression from gingivitis to periodontitis, and elevated HbA_{1c} is an important determinant of periodontal breakdown in both individuals with type 1 diabetes and those with type 2 diabetes [29–31], with a direct correlation between periodontal health and HbA_{1c} in persons with type 2 diabetes [19, 31–33]. Thus, well-managed diabetes is a prerequisite for maintaining periodontal health [34]. Moreover, the prevalence of periodontal sites with moderate to severe attachment loss also depends on the duration of diabetes [35]. Figure 56.7 illustrates the greater prevalence of moderate or severe periodontitis in people with sub-optimally or well-managed diabetes compared to individuals without diabetes. It appears that the prevalence of moderate or severe periodontitis in individuals with diabetes is about double that of those without and triple in the youngest group aged 30–44 years with sub-optimally managed diabetes compared to those without diabetes [36, 37].

To reduce the unrecognized course of periodontitis with tissue loss, it is advisable to establish a system that enables easy access to routine periodontal examination of persons with diabetes [1, 38].

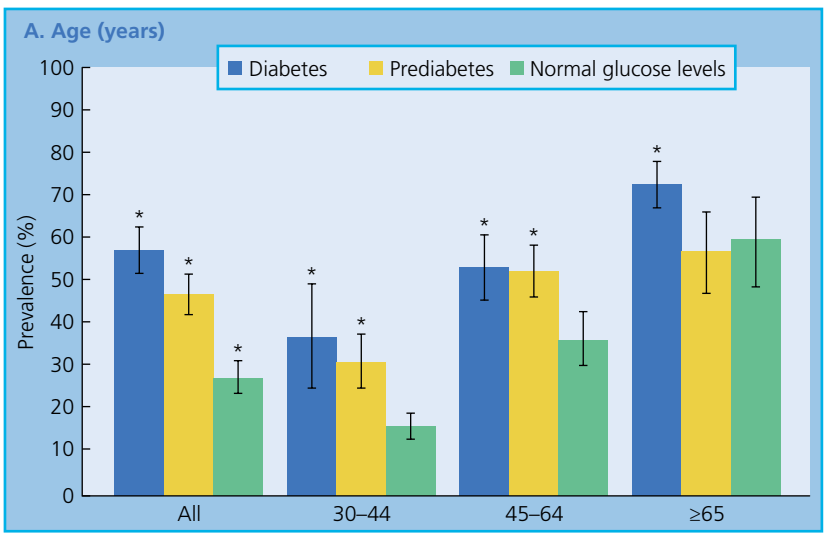

Figure 56.7 There is a greater prevalence of moderate or severe periodontitis in people with sub-optimally or well-managed diabetes compared to individuals without diabetes. Source: Reproduced by permission from Borgnakke et al. 2017 [36].

Dental health education and surveillance may be particularly important in this population, since sub-optimal metabolic management is often associated with poor oral hygiene [39].

Several studies and reviews have shown that periodontitis adversely affects blood glucose levels even with increased HbA_{1c} in individuals without diabetes [40, 41]. Elevated HbA_{1c} levels were more frequently seen in individuals examined in the dental clinic with periodontitis than in those without [42]. Thus, the more severe the periodontal condition, the poorer glycaemic status becomes, and the more diabetes-related complications are seen [2, 41, 43–45]. Analyses of data from a nationwide database in Taiwan have shown that people with severe periodontitis and in need of surgical treatment after confounder adjustment had a 23% increased risk of developing overt type 2 diabetes within a period of two years [46]. Studies from other countries have confirmed this finding [41]. Further clear evidence of the significance of periodontitis for the course of diabetes comes from clinical studies on the effect of periodontal treatment in individuals with diabetes (see later).

The counterpart to periodontitis around dental implants is denoted peri-implantitis. It is characterized by tissue breakdown including bone resorption around dental implants, with possible disintegration of the implant, and hyperglycaemia may also be associated with an increased risk of peri-implantitis like periodontitis [47, 48].

It can be concluded that well-managed diabetes does not imply an increased risk of attachment loss, but it is a challenge that both periodontitis and type 2 diabetes have a quiet, insidious course, and that many people do not know that they have periodontitis, pre-diabetes, or overt type 2 diabetes. Because the bidirectional interaction of the two diseases has a major impact on the affected individuals, dentists and medical doctors should be aware of the interaction of the diseases.

Pathogenic mechanisms linking diabetes and periodontitis

Diabetes and periodontitis, like several other inflammatory diseases, share several risk indicators including socioeconomic factors and smoking [49]. They also possess pathogenic similarity in their shared inflammatory background, which is why inflammatory interaction of the two diseases is an obvious possible driver of their mutual interaction.

A dysregulated immune system is central to the pathogenesis of diabetes and its associated complications. Systemic changes in cytokine levels have an impact on the pathogenesis of type 2 diabetes, which is associated with several physiological, nutritional, and metabolic changes, including hyperglycaemia, production of advanced glycation end-products (AGEs), hyperlipidaemia, and increased adiposity [50]. These mechanisms can contribute to the deterioration of the individual's periodontal condition [51]. Persistent hyperglycaemia results in glycation of proteins and eventually conversion to AGEs, which may lead to immune dysregulation with a long-lasting inflammatory state and a weakened self-limitation and resolution of immune responses, which are characteristic of periodontitis [51].

Many studies have investigated pathogenic pathways by which diabetes may have an impact on the course of periodontitis [52–55]. These include studies showing an impact of the level of hyperglycaemia in people with normoglycaemia or pre-diabetes as well as those with diabetes on the composition of the periodontal microbiota [56–58].

Clinical and animal studies have demonstrated elevated gingival levels of several factors that may all potentiate tissue destruction in people with sub-optimally managed diabetes. These include interleukin 1β (IL1-β), tumour necrosis factor α (TNF-α), IL-6, receptor activator of nuclear factor kappa B ligand (RANKL)/osteoprotegerin (OPG), and reactive oxygen species (ROS). In addition, individuals with diabetes and periodontitis exhibit high levels of both circulating TNF-α, C-reactive protein (CRP), and ROS, and successful periodontal treatment reduces these levels [55].

The binding of AGE to its receptor (RAGE) may result in the synthesis of pro-inflammatory cytokines, activation of nuclear transcription factor-κB (NF-κB), and production of ROS [59], all of which may result in increased cellular apoptosis, reduced bone formation, and increased bone resorption, as thoroughly reviewed [52–54]. A summarizing model of a mechanism of diabetes-related bone loss in periodontitis is presented in Figure 56.8 [52, 60].

Interaction of AGEs with toll-like receptors (TLRs) has been described, and increased expression of TLR2, TLR4, and TLR9 has been found in periodontitis-affected tissues of individuals with diabetes, compared to similar tissue from people without diabetes [61]. Further investigations of the TLR-mediated pathways in diabetes and periodontitis are obviously needed.

The role of neutrophils in the development of periodontitis in general is considered protective, and impaired neutrophil function may account for an increased susceptibility to periodontitis. Indeed, neutrophil function in individuals with diabetes and periodontitis has been studied intensively. The outcome of studies based on peripheral neutrophils may conceivably differ from that of neutrophils located in periodontal tissues. However, signs of compromised neutrophil function have been found in persons with type 2 diabetes and periodontitis [62].

Although an impact of periodontitis on diabetes may appear obvious, there is still limited evidence to understand the mechanistic pathways of periodontitis's influence on diabetes, while most is still speculative. Most studies demonstrate that circulating pro-inflammatory mediators are elevated in individuals with diabetes and periodontitis, in particular TNF-α, CRP, and mediators of oxidative stress. Taken together, these mediators may affect glycaemic levels [2].

High levels of CRP in individuals with both diabetes and periodontitis have been associated with increased HbA_{1c}, and since periodontitis itself may account for higher levels of CRP, the additional systemic inflammation associated with periodontitis may be responsible for the increased HbA_{1c} in individuals with diabetes and periodontitis [40]. Insulin resistance in people with periodontitis and diabetes may also be promoted by hyperreactive neutrophils producing ROS, which, in turn, may stimulate pro-inflammatory pathways [63]. An obvious similarity of the two diseases also includes an increased level of oxidative stress [64].

Experimental studies in rodents have provided insight into the possible interactions between periodontitis and diabetes [65]. Interestingly, ligature-induced periodontitis has been shown to deteriorate metabolic control in rats with type 2 diabetes, with an increase in glucose tolerance of 30% and an increase in IL-1β in adipose tissue compared to rats with diabetes, but without periodontitis [66]. In pre-diabetic rats with ligature-induced periodontitis glucose tolerance was also significantly impaired, which suggests that periodontitis may facilitate the development of overt diabetes [67]. Moreover, the pre-diabetic rats with periodontitis developed renal alterations including kidney hypertrophy and a tendency for increased glomerular volume [68].

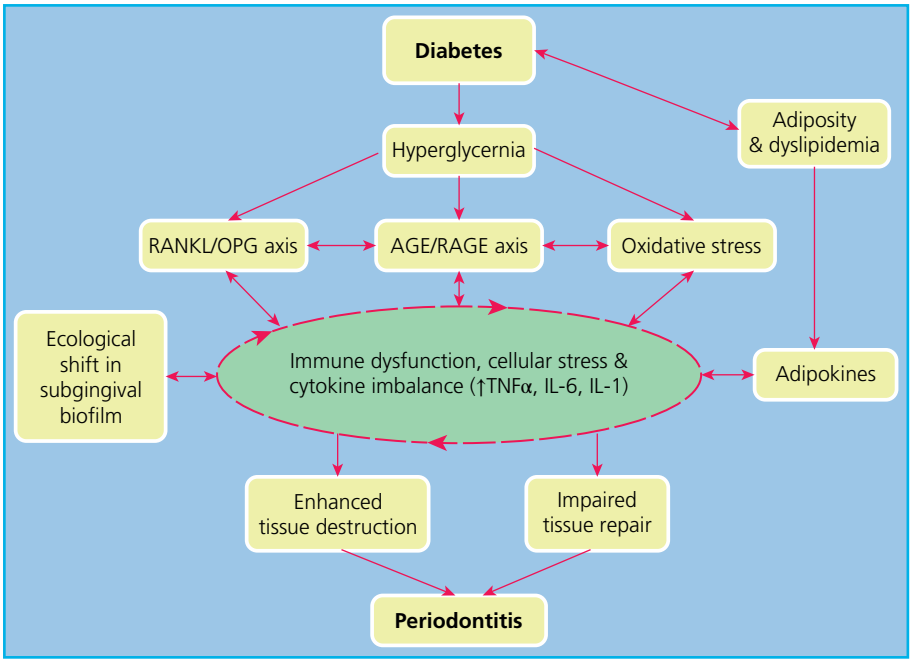

Figure 56.8 The network of potential mechanisms involved in the pathogenesis of periodontitis in diabetes. The hyperglycaemic state that characterizes diabetes has several deleterious effects. It drives the formation of irreversible advanced glycation end-products (AGEs) and the expression of their chief signalling receptor RAGE. This interaction, in turn, leads to immune dysfunction, alters the phenotype and function of other key cells in the periodontium, and contributes to cytokine imbalance with increased generation of certain pro-inflammatory cytokines. Hyperglycaemia also contributes to enhanced levels of reactive oxygen species (ROS) and a state of oxidative stress, both directly and indirectly through the AGE/RAGE axis, promoting quantitative and qualitative shifts in cytokine profiles. Finally, hyperglycaemia modulates the receptor activator of nuclear factor-κB ligand (RANKL)/osteoprotegerin (OPG) ratio, again directly and indirectly via the AGE/RAGE axis, tipping the balance towards enhanced inflammation and destruction. All of this, complemented by the effects of ecological shifts in the subgingival biofilm and the circulating adipokines generated due to diabetes-associated adiposity and dyslipidaemia, drive this vicious cycle of cellular dysfunction and inflammation. The end result is a loss of equilibrium where enhanced periodontal tissue destruction and impaired repair ensue, leading to accelerated and severe periodontitis. Importantly, as shown, several of the associations between the different elements in the figure are bidirectional, for example the pro-inflammatory state further feeds the generation of AGEs, ROS, and adipokines, increases the RANKL/OPG ratio, and helps pathogenic subgingival bacteria thrive. It is also important to note that the amount and quality of evidence supporting the various pathways in this figure vary, and that although the goal is to depict the major mechanisms and networks described in the literature, other pathways and links among the various elements shown do exist, but cannot easily be demonstrated in a single schematic. Finally, the processes outlined are potentially modified by several other factors, such as genetics, age, smoking, and stress, all of which may contribute significantly to inter-individual variations in disease experience. IL, interleukin; TNF, tumour necrosis factor. Source: Reproduced from Taylor et al. 2013 [52, 60] by permission of Wiley. © European Federation of Periodontology and American Academy of Periodontology.

Both the release of pro-inflammatory mediators and the presence of bacteria in the periodontal pockets, which, as the result of daily procedures such as chewing, tooth brushing, and flossing, may spread after penetration of the vasculature [69], are possible mediators of systemic consequences [20]. Moreover, as described for *P. gingivalis*, which is closely associated with periodontitis, microorganisms may evade attack from circulating phagocytes via so-called immune adherence by binding to complement receptor 1 at the surface of erythrocytes [70]. This means that *P. gingivalis* exploits erythrocytes as a transport vehicle, rendering it inaccessible to attack by phagocytes, thereby playing a role in the development of systemic diseases, for instance by increasing systemic low-grade inflammation, as previously shown by a higher plasma level of IL-6 [71].

Thus, pro-inflammatory cytokines produced locally in the inflamed periodontal tissues, where they are involved in tissue-destructive processes, may 'spill over' to the circulation. This as well as increased cytokine production due to bacteraemia may have a systemic impact and contribute to a state of elevated systemic low-grade inflammation [72–74]. Dysregulation of the cytokine production is also essential for the pathogenesis of diabetes [50]. Thus, both diabetes and periodontitis may be associated with increased systemic low-grade inflammation and pro-inflammatory cytokines, including TNF-α, IL-1-β, IL-6, and IL-18, which are increased in both diseases. Increased cytokine levels may contribute to insulin resistance and to diabetes-related complications, as well as to destruction of pancreatic β cells [75–78]. Interestingly, adipose tissue is an important source of cytokine production, and obesity may predispose to both type 2 diabetes and periodontitis [79–83], although the significance of obesity for periodontal tissue degradation is still to be resolved [84].

β cells from individuals with periodontitis produce a pro-inflammatory cytokine profile similar to that of β cells from individuals with type 2 diabetes [85]. Finally, hyperlipidaemia seems to interact with diabetes and periodontitis by increasing the risk of both diseases. The production of pro-inflammatory cytokines is increased by hyperlipidaemia, and this may aggravate both insulin resistance and periodontitis [86].

Periodontitis and late diabetes-related complications

A number of diabetes-related complications have been investigated in relation to periodontitis and a majority of the studies have shown a higher association or risk of severe periodontitis and late diabetes-related complications. After confounder adjustment, retinopathy appears to be significantly associated with periodontitis, and there are indications of a correlation of periodontitis severity with severity of retinopathy [2]. Periodontitis also appears to be significantly

associated with renal complications in both type 1 diabetes and type 2 diabetes. The occurrence of neuropathic foot ulceration has been associated with periodontitis too [2]. Both diabetes and periodontitis are independently associated with cardiovascular diseases. Therefore, it is not surprising that when the two diseases come together there is an increased risk of cardiovascular diseases. Thus, in type 2 diabetes cardiovascular complications appear to be significantly associated with periodontitis, and overall mortality is significantly higher in these individuals also suffering from periodontitis [2].

Significance of periodontal treatment for the course of diabetes

The treatment of gingivitis and periodontitis includes mechanical removal of dental biofilm and calculus. The responding reduction of clinical inflammation is followed by reduced systemic low-grade inflammation, as reflected in reduced inflammatory markers; that is, IL-6, TNF-α, and CRP in serum [87, 88]. The available scientific evidence indicates that individuals with diabetes can successfully receive periodontal treatment provided that effective self-care is conducted. Both clinical periodontal and local inflammatory measures improve after non-surgical treatment even in people with sub-optimally managed diabetes [2].

Many studies have examined the role of periodontal treatment for the course of diabetes, but long-term randomized clinical trials are scarce. The studies are characterized by different inclusion criteria, including various types of diabetes, with few individuals with type 1 diabetes included, and various diagnostic criteria for a case of periodontitis as well as various outcome measures. Moreover, stratification for confounders such as smoking, overweight, and medication is difficult. Meta-analyses of short-duration studies [88–90] indicate a positive effect on metabolic management of non-surgical periodontal treatment. This is particularly evident in individuals with type 2 diabetes. The meta-analyses showed that non-surgical periodontal treatment significantly reduced HbA_{1c} and fasting plasma glucose in people with diabetes. The mean decrease of HbA_{1c} was approximately 0.3–0.6% (3–6 mmol/mol) and the decrease in fasting plasma glucose was 9.0–13.6 mg/dl (0.5–0.8 mmol/l) after 3–6 months. Moreover, markers of systemic inflammation were reduced – that is, TNF-α (−1.33 ng/l) and hs-CRP (−1.28 mg/l) – but there was no positive effect of adjunctive antimicrobials. Interestingly, a recent well-conducted UK study, involving 264 individuals with diabetes and periodontitis followed for one year, showed that intensive periodontal treatment reduced HbA_{1c} by 0.6 percentage points (7 mmol/mol) compared with the control group after correction for background factors [91]. As another British study has shown that a 0.9 percentage point (10 mmol/mol) reduction in HbA_{1c} value can lead to a 10% reduction in mortality, such a reduction may be crucial for the course of diabetes [92].

A model-based cost-effectiveness analysis of periodontal treatment among individuals with type 2 diabetes has shown that providing non-surgical periodontal treatment for people with type 2 diabetes and periodontitis would likely have meaningful public health benefits. Substantial reductions in morbidity would most likely be observed, including reduced tooth loss and less microvascular disease via improved glycaemic management. Expanding periodontal treatment among individuals with type 2 diabetes would thus be cost saving or cost-effective [93, 94].

The reported effect of periodontal treatment has led to new guidelines from the National Health Service (NHS) in England emphasizing the importance of routine periodontal treatment of individuals with diabetes, as well as the importance of periodontal treatment in all people with periodontitis to prevent development of overt type 2 diabetes [38].

Globally, almost half (46.5%) of all people with type 2 diabetes (192.8 million) are estimated to be unaware of their disease [19, 95], and dentists may help reduce the number with undiagnosed type 2 diabetes. Dentists see their clients regularly, which provides an obvious opportunity for the identification of early signs of undiagnosed type 2 diabetes, such as altered courses of periodontal attachment loss and emerging infection (oral candidiasis). A Danish study showed that 3.1% of 291 examined individuals without diagnosed type 2 diabetes had HbA_{1c} values indicating the presence of type 2 diabetes. In addition, 27.1% had HbA_{1c} values above the limit value for pre-diabetes [42]. Individuals with periodontitis more frequently had elevated HbA_{1c} values than people without periodontitis. Periodontitis may therefore be an indicator of elevated HbA_{1c} and pre-diabetes or overt type 2 diabetes. Contributing to the early diagnosis of type 2 diabetes, in addition to the prevention of diabetes-related complications such as cardiovascular disease, neuropathy, and nephropathy, is important in reducing the increased risk of attachment loss and other diseases of the oral cavity.

Caries

Tooth decay is extremely common worldwide [13]. Among children and adolescents with type 1 diabetes the incidence of caries is very high (67%), and it is related to disease duration and the degree of hyperglycaemia [96]. Caries growth may be higher in children with dysregulated type 1 diabetes than in healthy children, but according to a systematic review [97] the evidence is inconclusive. Increased caries activity and experience might be associated with increased salivary glucose concentration, increased plaque incidence, and changes in the oral microbiota [98–100] as well as decreased salivary secretion rate and lower pH in saliva [100, 101]. Thus, several studies have shown that the incidence of carious teeth appears to be increased in individuals with diabetes [102, 103], including dysregulated type 2 diabetes [104]. A consequence of major destruction due to caries is tooth loss, but another result of deep caries is that the dental pulp tissue may be affected. This may not only result in pain but also in necrosis of the dental pulp tissue. The following leakage of toxins from the apical foramen to the periapical bone, inflammation known as periapical periodontitis (localized osteomyelitis), may occur and sometimes be followed by abscess formation. Individuals with sub-optimally managed diabetes seem to have an increased prevalence of periapical lesions compared to those with better-managed diabetes [105]. Endodontic treatment is necessary, including removal of the necrotic pulp tissue and after mechanical preparation of the root canals; they are filled with a material that closes the apical foramen. However, studies have indicated that diabetes appears to increase the extraction rate of such root-filled teeth [106].

Hyposalivation

Reduced secretion of saliva and xerostomia occurs often in persons with diabetes [107, 108]. An average reduction of 16% has been described in people with type 1 diabetes and as much as 54% in individuals with type 2 diabetes, in both cases after a disease duration of

10 years [109, 110]. The difference may be due to higher age in individuals with type 2 diabetes, with more late diabetes-related complications, a higher degree of comorbidity, and increased intake of xerogenic drugs than in people with type 1 diabetes. Hyposalivation associated with diabetes may be due to changes in the salivary glands due to hyperglycaemia or due to diabetic neuropathy, but probably polyuria may play a role as well. Hyposalivation may be associated with increased salivary glucose and mucin, which again may result in a change in viscosity. A reduced content of salivary antimicrobial substances may in addition to the reduced amount of saliva account for increased susceptibility to oral diseases, including caries and candidal infection. Lubricating and digestive properties are affected as well as speaking, chewing, and swallowing potentially being difficult. Halitosis and coated tongue are other associated characteristics [1]. Several studies have suggested that persons with diabetes also have a reduced taste perception and a higher electrical taste threshold than healthy individuals [111–113].

Candidal infection

In people with type 1 diabetes and type 2 diabetes an increased oral incidence of *Candida* species, especially *C. albicans*, has been related to hyperglycaemia [114], long diabetes duration, late diabetes-related complications (nephropathy and retinopathy), and smoking [115]. Also, in individuals with diabetes an increased susceptibility to manifest candidal infection is seen [114, 115], either manifest as classic oral candidiasis or as candida-associated lesions, including median rhomboid glossitis, denture stomatitis, and angular cheilitis [115]. The associated symptoms may be a burning sensation in the oral mucosa, a metallic taste, and dry mouth.

Oral cancer

Diabetes has been associated with an excess risk of cancer in several sites of the body. In the oral cavity various types of malignancy may occur, with squamous cell carcinoma accounting for the vast majority. A systematic review has summarized existing observational studies and found a 15-fold higher risk of oral cancer and pre-cancerous lesions in individuals with type 2 diabetes [116]. In general, there appears to be a higher excess risk in women compared with men. This also applies to oral cancer, the excess risk among women being 13% greater than among men [117]. The increased prevalence of candidiasis in individuals with diabetes [114, 115] may partly explain why pre-malignant lesions of the oral mucosa also appear to be slightly more common [118, 119].

Guidelines for physicians and other medical health professions for use in practice

Because of the increased risk of developing periodontitis in individuals with diabetes and the negative impact of periodontitis on hyperglycaemia and complications, the IDF and the EFP have established the following set of recommendations, which may be helpful in daily practice. The guidelines also apply to people with pre-diabetes and the metabolic syndrome [2]:

- Oral health education should be provided to all individuals with diabetes as part of their overall educational programme.
- People with all forms of diabetes should be told that periodontal disease risk is increased, and that, if untreated, periodontitis has a negative impact on metabolic management and may also increase the risk of diabetes complications such as cardiovascular and kidney disease.
- Persons with diabetes should be advised that successful periodontal therapy may have a positive impact on their glycaemic management and risk of late diabetes complications.
- For people with diabetes, physicians should ask about a prior diagnosis of periodontal disease. If a positive diagnosis has been made, the physician should seek to ascertain that periodontal care and maintenance are being provided. Investigating the presence of periodontal disease should be an integral part of a diabetes care visit. People with diabetes should be asked about any signs and symptoms of periodontitis, including bleeding gums during brushing or eating, loose teeth, spacing or spreading of the teeth, oral malodour, and/or abscesses in the gums or gingival suppuration.
- If a positive history is elicited, then a prompt periodontal evaluation should be recommended before their scheduled annual check-up. In the case of a negative history, people with diabetes should be advised to check for these symptoms, and if a positive sign appears they should visit their dentist.
- For all people with newly diagnosed diabetes, referral for a periodontal examination should occur as part of their ongoing management of the diabetes. Even if no periodontitis is diagnosed initially, annual periodontal review is recommended.
- For children and adolescents diagnosed with diabetes, annual oral screening is recommended through referral to a dental professional.
- People with diabetes who have extensive tooth loss should be encouraged to pursue dental rehabilitation to restore adequate mastication for proper nutrition.
- People with diabetes should be advised that other oral conditions such as dry mouth and burning mouth may occur, and if so they should seek advice from their dental practitioner. Also, individuals with diabetes are at increased risk of oral fungal infections and experience poorer wound healing than those without diabetes.
- The physician should liaise with the dentist over diabetes management prior to the oral intervention and/or surgery to avoid hypoglycaemia and consider its potential impact on the patient's ability to eat.

Collaboration in healthcare for the benefit for persons with diabetes

Individuals with diabetes may have limited knowledge about the significance of oral health [118] and in some countries individuals with diabetes appear to visit their dentist less frequently than people without diabetes [39, 121, 122]. Therefore, an intensified effort emphasizing the importance of regular oral home care, dental examination, and treatment may be necessary. This is why a new strategy is important, a strategy that can be accomplished only by interprofessional collaboration in healthcare for persons with diabetes [123]. Hopefully, medical and dental professionals will understand the significance and benefit of regular dental care for these patients. A fruitful collaboration is based on knowledge, and there may be a need to intensify exchange of knowledge between medical and dental professionals [124] to facilitate an active role by medical

care professionals in addressing oral health in their patients, as well as a more active role of dental professionals in identifying individuals with undiagnosed diabetes [42, 125]. In a study from the USA, screening for diabetes in the dental setting was effective in identifying pre-diabetes and type 2 diabetes [126] and early detection led to instigation of cost-effective lifestyle change measures, which resulted in a significant proportion of patients moving from pre-diabetes to normoglycaemia. In the UK, the National Institute of Health and Care Excellence has suggested that healthcare professionals other than physicians, including dentists, should be screening for undiagnosed type 2 diabetes [2].

Conclusion

The association between periodontitis and diabetes has been described as bidirectional, and there is substantial evidence that hyperglycaemia in type 1 diabetes and type 2 diabetes adversely affects periodontitis, resulting in increased extension and severity of periodontitis. Due to the global increase in the prevalence of diabetes, the influence of diabetes on the development of periodontitis may be a growing problem. Current evidence also suggests that periodontitis may have a negative impact on the course of diabetes. The mechanisms by which the two diseases interact are uncertain, but presumably systemic low-grade inflammation enhanced by both diseases play an important part in their interaction, which obviously involves inflammatory cells and their products. In addition, the formation of AGEs results in modified cellular functions, with a possible negative impact on periodontitis.

The existing clinical trials indicate a positive effect on metabolic management and systemic inflammation of non-surgical periodontal treatment, which may result in a clinically relevant decrease of HbA_{1c}. Intensive prevention and treatment of gingivitis and caries in children and adolescents with type 1 diabetes with elevated HbA_{1c} are also essential to prevent further progression of these conditions.

Individuals with diabetes and decreased salivary secretion are recommended to have frequent, regular dental check-ups and cleaning to prevent the development of caries. Early intervention for special-risk individuals, such as children and young people with obesity, including dietary guidelines to reduce sugar intake, may help reduce the risk of developing not only obesity but also caries. It should also be remembered that people with elevated HbA_{1c} may lack oral hygiene, and they may visit the dentist more infrequently than those with better glycaemic management. Regular examination of oral health is important for the identification of candidal infection, oral pre-malignant lesions, and manifest malignancy, which all appear to be more common in persons with diabetes than in healthy individuals.

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57 Diabetes and Non-alcoholic Fatty Liver Disease

Alessandro Mantovani[1], Giovanni Targher[1], and Christopher D. Byrne[2,3]

[1] Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University of Verona, Verona, Italy

[2] Nutrition and Metabolism, Faculty of Medicine, University of Southampton, Southampton, UK

[3] Southampton National Institute for Health and Care Research Biomedical Research Centre, University Hospital Southampton, Southampton General Hospital, Southampton, UK

Key points

- Non-alcoholic fatty liver diseases (NAFLD) embraces a spectrum of lipid-associated liver conditions, extending from simple steatosis (or NAFLD) to non-alcoholic steatohepatitis (NASH) (both with and without liver fibrosis), to cirrhosis.
- NAFLD is defined by the presence of macrovesicular steatosis in ≥5% of hepatocytes in individuals who consume little or no alcohol, without evidence of hepatocellular injury. NASH is defined by the presence of ≥5% macrovesicular steatosis plus inflammation with hepatocyte injury (ballooning), both with and without any liver fibrosis.
- NAFLD is one of the commonest causes of liver disease worldwide, affecting up to 70% of people with type 2 diabetes.
- Age, sex, ethnicity, some genetic variants, and metabolic risk factors (e.g. obesity and type 2 diabetes) can interact to increase the risk of development and progression of NAFLD.
- Individuals with type 2 diabetes are at higher risk of developing the more advanced forms of NAFLD, including NASH, cirrhosis, liver failure, and hepatocellular carcinoma.
- The presence of NAFLD in people with type 2 diabetes is associated with higher glycated haemoglobin (HbA_{1c}) concentration and greater hepatic and peripheral insulin resistance.
- NAFLD is associated not only with liver-related morbidity and mortality, but also with an increased risk of developing type 2 diabetes, cardiovascular disease (which is the predominant cause of mortality in people with NAFLD), chronic kidney disease, and certain types of extrahepatic cancers (especially colorectal cancer).
- NAFLD exacerbates insulin resistance, predisposes to atherogenic dyslipidaemia, and causes the release of pro-inflammatory, procoagulant, and proatherogenic factors that have a role in the development of chronic vascular complications of diabetes.
- There are no licensed pharmacological treatments specifically for liver disease in NAFLD. Management is based on promoting weight loss by diet and exercise, controlling all coexisting cardiometabolic risk factors, and preventing the development and progression of liver-related and extrahepatic complications.
- Bariatric surgery improves all of the histological features of NAFLD, including liver fibrosis, and is indicated for people with type 2 diabetes and severe obesity.
- Among glucose-lowering agents, pioglitazone and glucagon-like peptide 1 (GLP-1) receptor agonists (e.g. subcutaneous semaglutide) may improve NASH without worsening liver fibrosis. Sodium–glucose transporter 2 (SGLT-2) inhibitors may be a future treatment option for NAFLD.
- Among newer drugs for NASH, obeticholic acid, a synthetic analogue of chenodeoxycholic acid, can improve both NASH and fibrosis, but increases plasma low-density lipoprotein cholesterol concentrations.

Non-alcoholic fatty liver disease (NAFLD) is a metabolic liver disease that includes a spectrum of progressive pathological conditions, ranging from simple steatosis (or non-alcoholic fatty liver, NAFL) to non-alcoholic steatohepatitis (NASH) and cirrhosis [1, 2]. NAFLD has become one of the most common causes of chronic liver disease worldwide, affecting up to ~30% of adults in the general population [3], up to ~70% of individuals with type 2 diabetes [4], and up to ~35% of adults with type 1 diabetes [5].

Although the pathophysiology of this common liver disease is multifaceted, a large body of evidence indicates that NAFLD and type 2 diabetes frequently coexist. When both conditions do coexist, a 'vicious' cycle occurs with either condition adversely affecting the other to increase the risk of developing liver-related and extrahepatic complications [5–9]. In addition, it has become increasingly clear that there is an intimate bidirectional relationship between NAFLD and type 2 diabetes, and that NAFLD may precede and/or promote the development of type 2 diabetes over time [10, 11]. Notably, given the close inter-relationships between NAFLD, obesity, and type 2 diabetes, a change in the terminology of NAFLD has been recently proposed, changing the name for this common liver disease from NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD) [12, 13]. Within this newly proposed terminology, the diagnosis of MAFLD is primarily based on the presence of hepatic steatosis (assessed by liver biopsy, imaging techniques, or blood biomarkers/scores) and at least one of the following three metabolic abnormalities: overweight/obesity, pre-existing type 2 diabetes, or metabolic dysregulation (i.e. the coexistence of at least two metabolic risk factors among those

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typically used for diagnosing the metabolic syndrome: increased waist circumference, increased blood pressure, high triglycerides, low high-density lipoprotein (HDL) cholesterol, impaired fasting glycaemia, *plus* homeostasis model assessment-insulin resistance or increased plasma C-reactive protein (CRP) concentrations) [12, 13]. The newly proposed definition of MAFLD emphasizes that overweight/obesity, type 2 diabetes, and other metabolic risk factors are key factors in the development of this common and burdensome liver disease [14–16]. Moreover, given that increasing evidence now suggests that a safe threshold for daily alcohol consumption is close to zero, the use of a term (like non-alcoholic) based on the exclusion of a risk factor might be oversimplified [14–16]. Finally, the definition of MAFLD might also improve the identification of people at higher risk of liver-related and cardiometabolic complications [16, 17]. However, since it is currently still debated which term should be used, and as some experts [18, 19] consider that a change in the terminology of NAFLD may be premature at this time, in this chapter we consider it appropriate to discuss 'NAFLD' and not 'MAFLD'.

Specifically, in this chapter, we will discuss the definition, diagnosis, and epidemiology of NAFLD (in the context of type 2 diabetes); the aetiology and pathogenesis of NAFLD; the main extrahepatic complications of NAFLD; and the treatment for NAFLD in people with type 2 diabetes with or without coexisting cardiovascular disease (CVD). The relationship between NAFLD and type 1 diabetes is not discussed in this chapter, as research on this topic is still limited.

Non-alcoholic fatty liver disease definition, epidemiology, and diagnosis

Definition

Non-alcoholic fatty liver (NAFL) is defined by the presence of macrovesicular steatosis in ≥5% of hepatocytes in individuals who consume little or no alcohol, without evidence of hepatocellular injury in the form of hepatocyte ballooning [1, 2]. Non-alcoholic steatohepatitis (NASH) is defined as the presence of ≥5% macrovesicular steatosis and inflammation with hepatocyte injury (ballooning), with or without any stage of liver fibrosis [1, 2]. There are five histological stages of liver fibrosis in NAFLD: F0 = no fibrosis; F1 = perisinusoidal fibrosis; F2 = portal fibrosis; F3 = 'bridging' fibrosis; and F4 = cirrhosis [1, 2].

Non-alcoholic fatty liver disease epidemiology in type 2 diabetes

Across the spectrum of hepatic disease in NAFLD, NAFL, NASH, advanced fibrosis, and cirrhosis occur more frequently in people with type 2 diabetes compared with those without diabetes [4, 6]. Indeed, population-based studies and hospital-based ones have reported that the prevalence of NAFLD (as detected by imaging techniques or biopsy) in individuals with type 2 diabetes ranges from 30% to 70% and from 50% to 70%, respectively [20–30]. These wide inter-study differences are largely due to the clinical characteristics of the study populations and the techniques used for the diagnosis of NAFLD.

The high prevalence of NAFLD in people with type 2 diabetes was confirmed in a systematic review and meta-analysis of 80 observational studies showing that the global prevalence of NAFLD (on imaging techniques or histology) in people with type 2 diabetes was approximately 55%, whereas the global prevalence of more advanced forms of NAFLD, such as NASH and advanced fibrosis (on liver histology), was 37% and 17%, respectively [4]. As shown in Table 57.1, the global prevalence of NAFLD varied between different countries (with the highest prevalence observed in Europe) [4]. Different ethnic groups have also disparate propensities to NAFLD, with Hispanic individuals being more susceptible than people of white Northern European ancestry, whereas the lowest susceptibility is observed in Black individuals [31].

Table 57.1 Global and regional prevalence of non-alcoholic fatty liver disease (NAFLD, as detected by imaging techniques) in people with type 2 diabetes [4].

Regions	NAFLD prevalence	95% confidence intervals
Worldwide	55.5%	47.3 to 63.7%
USA	51.8%	31.3 to 71.6%
Europe	68.0%	62.1 to 73.0%
Latin America	56.8%	34.1 to 77.0%
East Asia	52.0%	45.4 to 58.6%
South Asia	57.9%	52.9 to 62.7%
West Asia	67.3%	60.4 to 73.6%
Africa	30.4%	11.6 to 67.1%

Diagnosis

NAFLD is essentially a diagnosis of 'exclusion' based on the following criteria (Table 57.2):

- Evidence of hepatic steatosis on liver histology, imaging techniques, or blood biomarkers/scores.
- No excessive alcohol consumption (a threshold of 20 g/d for women and 30 g/d for men is conventionally adopted).
- No other competing causes for hepatic steatosis, such as viral hepatitis, drug use, haemochromatosis, autoimmune hepatitis, and others [1, 2, 32].

Table 57.2 also summarizes the main differences in the diagnostic criteria for NAFLD and MAFLD.

Diagnosis of liver fat (steatosis)

The gold-standard method for diagnosing and staging NAFLD is liver biopsy [1, 2, 32]. However, liver biopsy is expensive, invasive, uncomfortable and inconvenient for the person undergoing the procedure, and potentially risky (serious bleeding may occur in 0.6% of cases, and death in 0.1%) [1, 2, 32, 33]. For these reasons, liver biopsy is not widely used for the diagnosis of NAFLD, nor in the monitoring of progression or resolution of the disease in clinical practice. However, it should be remembered that NASH can currently be diagnosed only by liver biopsy. Furthermore, liver biopsy should be considered when there is diagnostic uncertainty and other chronic liver diseases cannot be definitively excluded [1, 2, 32].

As summarized in Table 57.3, liver ultrasonography is the most widely used imaging technique to diagnose hepatic steatosis in clinical practice [1, 2, 32, 34]. A large meta-analysis showed that ultrasonography has good sensitivity (~85%) and specificity (~95%) for detecting moderate to severe hepatic steatosis, when compared to liver histology [35]. However, it is important to underline that the sensitivity of this imaging technique is relatively poor, when hepatic fat infiltration is present in <20% of hepatocytes [1, 2, 32, 34]. A diagnosis of hepatic steatosis on ultrasonography is established when liver echogenicity exceeds that of renal cortex and spleen; there is attenuation of the ultrasound signal; there is loss of

Table 57.2 Differences in the diagnostic criteria for non-alcoholic fatty liver disease (NAFLD) and metabolic dysfunction-associated fatty liver disease (MAFLD).

NAFLD [1, 2]	MAFLD [12, 13]
Hepatic steatosis (assessed by liver biopsy, imaging techniques, or blood biomarkers/scores[a])	Hepatic steatosis (assessed by liver biopsy, imaging techniques, or blood biomarkers/scores[a])
No significant alcohol consumption (a threshold of 20 g/d [~140 g/wk] for women and 30 g/d [~210 g/wk] for men is usually adopted)	One of the following metabolic criteria: • Overweight or obesity • Type 2 diabetes • Metabolic dysregulation[b]
No other known causes of hepatic steatosis: viral hepatitis B and C, drugs (e.g. chronic use of amiodarone, corticosteroids, methotrexate, oestrogens, valproic acid, tamoxifen, tetracycline, perhexiline maleate, 4,4′-diethylaminoethoxyhex esterol, chloroquine, L-asparaginase), haemochromatosis, autoimmune hepatitis, Wilson's disease, alpha 1 anti-trypsin deficiency, coeliac disease, and others (e.g. malnutrition, total parenteral nutrition, rapid weight loss, surgically altered bowel anatomy, lipodystrophy, hypobetalipoproteinaemia)	Exclusion of significant alcohol consumption and other secondary causes of hepatic steatosis is *not* a prerequisite for the diagnosis of MAFLD. Individuals with MAFLD who also have one (or more) of these conditions should be defined as having dual (or more) aetiology of fatty liver disease

[a] Serum biomarker scores for hepatic steatosis are Fatty Liver Index (FLI, an algorithm-derived score using body mass index, waist circumference, fasting serum triglycerides, and γ-glutamyltransferase concentrations) and NAFLD liver fat score (an algorithm-derived score using the presence of metabolic syndrome, type 2 diabetes, fasting serum insulin, serum aspartate transaminase (AST) levels, and the AST/alanine transaminase (ALT) ratio). For more details see Byrne et al. 2018 [32].
[b] At least two metabolic risk abnormalities among increased waist circumference (i.e. ≥102/88 cm in white European men and women or ≥90/80 cm in Asian men and women), increased blood pressure (i.e. blood pressure ≥130/85 mmHg or drug treatment), hypertriglyceridaemia (i.e. plasma triglycerides ≥150 mg/dl or drug treatment), low high-density lipoprotein (HDL) cholesterol (i.e. plasma HDL <40 mg/dl for men and <50 mg/dl for women or drug treatment), pre-diabetes (i.e. fasting plasma glucose levels from 100 to 125 mg/dl or 2 h post-load plasma glucose levels from 140 to 199 mg/dl or glycated haemoglobin (HbA_{1c}) from 39 to 47 mmol/mol), insulin resistance (i.e. Homeostatic Model Assessment of Insulin Resistance [HOMA-IR] ≥2.5) and/or increased plasma high sensitivity C-reactive protein concentrations (plasma hs-CRP >2 mg/l).

definition of the diaphragm; and there is poor delineation of intrahepatic architecture [32, 34].

The controlled attenuation parameter (CAP), assessed by vibration-controlled transient elastography (FibroScan®, Echosens, Paris, France), can also be used in clinical practice for diagnosing hepatic steatosis, but it is currently unclear what CAP thresholds should be used for the diagnosis of steatosis [32, 34]. Moreover, CAP measurement could be unreliable in individuals with severe obesity [32, 34].

Computed tomography has also been used to detect hepatic steatosis [1, 2, 32, 34]. However, this imaging technique has limited sensitivity to detect low levels of liver fat (<20–30%) and it exposes the person to ionizing radiation [32, 34]. For these reasons, computed tomography is not routinely used in clinical practice for diagnosing NAFLD [32].

Magnetic resonance imaging–proton density fat fraction (MRI-PDFF) and proton magnetic resonance spectroscopy (MRS) have excellent diagnostic accuracy for identifying hepatic steatosis and measuring intrahepatic fat content [1, 2, 32, 34]. Specifically, MRS enables accurate quantification of the hepatic triglyceride content. However, these two magnetic resonance–based techniques are expensive and not easily available, and therefore they are not routinely used in clinical practice for diagnosing NAFLD [1, 2, 32, 34].

Although hepatic steatosis may be associated with mild to moderate elevations of serum liver enzymes (mostly serum aminotransferase and/or gamma-glutamyltransferase [GGT] levels), it is important to note that most people with NAFLD (even if NASH or cirrhosis is present) have normal or only mildly abnormal serum liver enzymes. Therefore, measurement of serum liver enzymes alone should not be used for diagnosing or excluding the presence of NAFLD [1, 2, 32]. In the last decade, serum biomarker scores have been developed to identify NAFLD [1, 2, 32]. Fatty liver index (FLI) is one of the most widely used scores for diagnosing hepatic steatosis that includes in its equation body mass index (BMI), waist circumference, serum triglycerides, and GGT concentrations [1, 2, 32]. A FLI ≥60 is highly suggestive of hepatic steatosis on ultrasonography [32, 36, 37]. NAFLD liver fat score is another algorithm-derived score using the presence of metabolic syndrome, type 2 diabetes, serum fasting insulin, and aminotransferase levels. A cut-off point ≥−0.64 is highly suggestive of imaging-defined hepatic steatosis [32, 38]. However, it should be noted that neither of these two biomarker scores of hepatic steatosis has been validated against liver biopsy [32].

Diagnosis of liver fibrosis

Growing evidence indicates that individuals with NAFLD and advanced fibrosis are those at highest risk of developing liver-related and extrahepatic complications, as well as having the highest rates of all-cause and cause-specific mortality (mainly due to liver disease, CVD, and cancer) [1, 2, 5, 8, 39]. In a large meta-analysis of 45 observational studies involving more than 8 million people, followed for a period ranging from 4 to 13 years, the pooled all-cause mortality incidence rate among individuals with NAFLD was 15 per 1000 person-years, whereas among those with NASH with varying stages of fibrosis the pooled all-cause mortality incidence rate was 26 per 1000 person-years [3]. Notably, in a population-based cohort study of 12 253 US middle-aged individuals who were followed for a median of 23 years, Alvarez et al. showed that nearly 8% of all-cause mortality and more than 30% of liver disease-specific and diabetes-specific deaths were attributable to NAFLD [40]. In that study, the attributable risk of NAFLD for diabetes mortality was nearly 40%, whereas the population-attributable fraction (which is the contribution conveyed by a risk factor to a disease or a death) of NAFLD for both CVD and cancer mortality was approximately 10% [40]. That said, there is now strong evidence from the recent results of a nationwide matched-cohort study in Sweden showing that all histological

Table 57.3 Imaging techniques for diagnosing non-alcoholic fatty liver disease.

Imaging techniques	Characteristics	Main advantages	Main limitations
	Hepatic steatosis		
Ultrasonography	Recommended first-line imaging technique Liver echogenicity caps that of renal cortex and spleen, attenuation of the ultrasound wave, loss of definition of the diaphragm, poor delineation of the intrahepatic architecture	Inexpensive Non-invasive "Patient friendly" Widespread	Unable to detect mild steatosis Steatosis and fibrosis can have similar appearance Operator dependent Unreliable in individuals with severe obesity
Vibration-controlled transient elastography (FibroScan®) with controlled attenuation parameter (CAP)	Optimal CAP threshold ≥248 dB/m for diagnosing hepatic steatosis	Inexpensive Non-invasive "Patient friendly" Promising technique	Unable to detect mild steatosis Operator dependent Unreliable in people with severe obesity
Computed tomography	Attenuation of the liver is at least 10 Hounsfield units (HU) less than that of the spleen Attenuation of the liver less than 40 HU	Useful for investigating additional abdominal pathologies	Unable to detect mild steatosis High levels of radiation
Magnetic resonance imaging–proton density fat fraction (MRI-PDFF)	Chemical shift gradient echo imaging with in-phase and opposed-phase acquisitions Able to detect liver fat accumulation ≥5.5% (or less)	Non-invasive Sensitive for liver fat	Expensive Limited availability
Magnetic resonance spectroscopy (proton MRS)	Accurate quantification of liver fat accumulation (≥5.5% or less)	Non-invasive Sensitive for liver fat	Expensive Not easily available
	Hepatic fibrosis		
Vibration-controlled transient elastography (FibroScan® with the use of M probe or XL probe for severely obese individuals)	Measures a volume of the liver that is ~100 times larger than a liver biopsy sample Speed of propagation is in relation to the stiffness of the tissue Specific software Advanced fibrosis threshold (liver stiffness ≥9.7 kPa)	Non-invasive "Patient friendly" Immediate results XL probe has been validated for people with severe obesity	Expensive Limited in the setting of congestive hepatopathy or ascites Operator dependent
Acoustic radiation force impulse elastography (ARFI)	Advanced fibrosis threshold (ARFI >1.4 m/s)	Integrated into a conventional ultrasonography	Cut-off values for advanced fibrosis may vary Unreliable in people with severe obesity
Magnetic resonance elastography (MRE)	Advantages of MR with elastography	Accurate also in people with obesity Assesses the entire liver	Expensive Time consuming Limited availability

stages of liver disease in NAFLD are associated with increased risk of overall mortality, and that this risk increases progressively with worsening NAFLD histology. Most of this excess mortality is primarily from extrahepatic cancers, followed by cirrhosis, CVD, and hepatocellular carcinoma (HCC) [41].

Although liver biopsy is the reference standard for the assessment of liver fibrosis, the inherent limitations of this invasive procedure, and the need for repeat sampling, have led to the development of several non-invasive tests as alternatives to liver biopsy. Some of these non-invasive algorithmically derived scores for the assessment of liver fibrosis can be useful for identifying clinically significant fibrosis in individuals who may require a liver biopsy [32]. The Enhanced Liver Fibrosis (ELF) is a commercial algorithmically derived score using measurement of serum tissue inhibitor of matrix metalloproteinase-1, hyaluronic acid, and the amino-terminal peptide of pro-collagen III [32]. The ELF test has excellent performance for identifying NAFLD with a high probability of advanced fibrosis [32]. A 2014 meta-analysis confirmed that the ELF test performs well in the prediction of advanced fibrosis (F3 and F4 fibrosis) in NAFLD [42]. The NAFLD fibrosis score (NFS) is the most widely validated non-invasive test and it is calculated as follows [43]:

$$\text{NFS} = -1.675 + 0.037 \times \text{age} + 0.094 \times \text{BMI} + 1.13 \times \text{impaired fasting glycaemia or diabetes status (yes = 1, no = 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelet count} - 0.66 \times \text{serum albumin}$$

AST is aspartate transaminase and ALT is alanine transaminase. The NFS has adequate performance for identifying individuals with any grade of liver fibrosis, but poorer performance for diagnosing advanced fibrosis [32, 43]. A cut-off point >0.676 is highly suggestive of advanced fibrosis [43]. The Fibrosis (FIB)-4 score is another validated non-invasive test for identifying individuals who are expected to have significant fibrosis. This score is calculated as follows:

$$(\text{age} \times \text{AST})/(\text{platelet count} \times \sqrt{\text{ALT}})$$

A cut-off point >2.67 is indicative of advanced fibrosis [32]. Notably, all these non-invasive scores of fibrosis have a modest positive predictive value for identifying advanced fibrosis, and a good negative predictive value, such that they are currently recommended for ruling out advanced fibrosis rather than for diagnosing it [32]. Importantly, algorithmically derived biomarker scores are not good for identifying intermediate stages of liver fibrosis (F1–F2 stages) [32] and therefore, as also suggested by the recent guidelines from important scientific hepatology societies (the European Associations for the Study of the Liver, Diabetes, and Obesity [EASL-EASO-EASD] and the American Association for the Study of Liver Diseases [AASLD]) [1, 2], these non-invasive scores of fibrosis should be used only in a staged approach, and liver biopsy may be required if it is necessary to stage the severity of liver fibrosis or if there is diagnostic uncertainty [32].

Vibration-controlled transient elastography (FibroScan® with the use of M or XL probes for individuals with severe obesity) is a widely used technique to non-invasively stage hepatic fibrosis in clinical practice [32, 34]. This imaging technique measures the velocity of a low-frequency elastic shear wave propagating through the liver [32, 34]. This velocity is directly related to tissue stiffness [32]. The stiffer the tissue, the faster the shear wave propagates [32, 34]. Advantages of this technique include a short procedure time, instant results, and the possibility of performing the test in an outpatient clinic [32, 34]. Conversely, an important limitation of this methodology is its poor capacity to obtain reliable liver stiffness measurements in some individuals, especially people with severe obesity or ascites [32, 34]. Liver elasticity–based imaging techniques are being developed, including 2D acoustic radiation force impulse imaging (ARFI), shear-wave elastography, and 3D magnetic resonance elastography, but these techniques are mostly used in research at the present time (Table 57.3) [32, 34].

The EASL-EASO-EASD jointly and the AASLD have produced guidelines for the diagnosis, monitoring, and management of suspected NAFLD and coexisting metabolic risk factors [1, 2]. Ideally, all individuals with type 2 diabetes should undergo assessment with measurement of serum aminotransferase levels, liver ultrasonography, and measurement of non-invasive scores of fibrosis. Presently, however, there is debate regarding the most appropriate algorithm for diagnosis and monitoring of NAFLD in type 2 diabetes [7]. Figure 57.1 shows a pragmatic algorithm for the diagnosis and monitoring of NAFLD in people with type 2 diabetes [7]. Individuals with type 2 diabetes should be assessed (every 2–3 years) for the presence of NAFLD [7]. Since measurement of serum aminotransferase levels is not useful for the diagnosis or monitoring of NAFLD and most individuals with type 2 diabetes and NAFLD have normal serum liver enzyme levels, serum aminotransferase levels should not be used in isolation [7]. As mentioned, ultrasonography is the recommended first-line imaging technique for the diagnosing of hepatic steatosis in NAFLD [7]. Non-invasive assessment of advanced fibrosis by using specific non-invasive biomarkers (e.g. the FIB-4 score, NFS, or ELF test) can be used initially, followed by vibration-controlled transient elastography (FibroScan®) when the biomarker scores are above a certain threshold, in order to identify individuals with NAFLD and significant fibrosis (≥F2 fibrosis). Where there is diagnostic uncertainty or where it is important to stage liver fibrosis precisely, a liver biopsy should be undertaken.

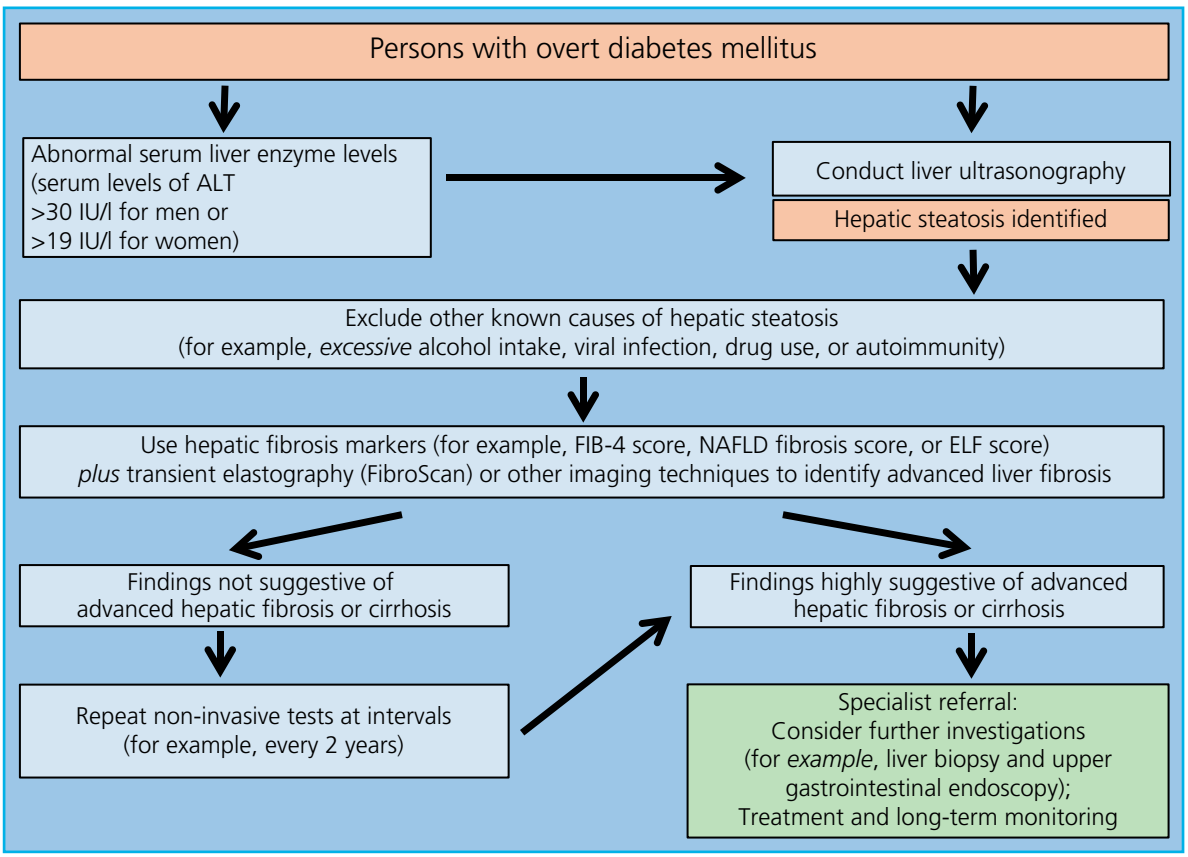

Figure 57.1 Possible pragmatic algorithm for the diagnosis and monitoring of non-alcoholic fatty liver disease (NAFLD) in persons with overt type 2 diabetes. ALT, alanine transaminase; ELF, Enhanced Liver Fibrosis; FIB-4, Fibrosis-4. Source: Modified by permission from Targher et al. [7].

Table 57.4 Typical case presentation of a person with type 2 diabetes and non-alcoholic fatty liver disease (NAFLD).

Case presentation
At a routine health check, a 67-year-old man with established type 2 diabetes was found to have a serum alanine aminotransferase (ALT) level of 66 IU/l (normal 0–40 IU/l), a serum aspartate aminotransferase (AST) level of 72 IU/l (normal 0–40 IU/l; AST/ALT ratio 1.1), and a triglyceride concentration of 2.1 mmol/l (186 mg/dl; normal value <150 mg/dl). Glycated haemoglobin (HbA_{1c}) was of 8% (64 mmol/mol). Other liver function tests, kidney function measures (serum creatinine and albuminuria), as well as other lipid blood tests (including low-density lipoprotein [LDL] cholesterol) were normal. There was no past medical history of viral hepatitis (i.e. hepatitis B or C virus infection) nor pre-existing history of cardiovascular disease or chronic kidney disease. He was treated with metformin (1000 mg twice a day) and ramipril (5 mg/d); he smoked (~10 cigarettes daily) and consumed <4 units of alcohol/wk. Clinical examination revealed moderate hepatomegaly, obesity (body mass index 30 kg/m^2; waist circumference 107 cm), and blood pressure 144/90 mmHg.
How should this man be investigated?
Investigation and management
The man has established type 2 diabetes and moderately elevated levels of serum transaminases without other secondary causes of chronic liver disease, including excessive alcohol intake, viral hepatitis B or C, or use of potentially hepatotoxic drugs. As suggested by current guidelines, persons with type 2 diabetes should undergo liver assessment by abdominal ultrasonography along with liver enzymes. The liver ultrasonography documented a moderate–severe hepatic steatosis. Hence, a diagnosis of NAFLD should be made. Since the individual has type 2 diabetes, obesity, hypertriglyceridaemia, and hypertension, a liver stiffness measurement (LSM), using vibration-controlled transient elastography (FibroScan®), should also be performed. The FibroScan® documented an LSM value of 8.7 kPa, which is strongly indicative of significant liver fibrosis (≥F2 fibrosis). We would strongly reinforce lifestyle recommendations, such as a programme of regular aerobic exercise (a gradual increase to 30 min of aerobic activity 5 d/wk), weight loss (with a 5–10% weight loss as target), a moderate restriction of sodium intake (e.g. 80–120 mmol/d, corresponding to 4.6–6.9 g of salt), and the substitution of sources of polyunsaturated fats (PUFAs), including oils (mainly olive), nuts, cold-water fish, and shellfish for saturated fats and simple carbohydrates. Given that the man smokes, we should advise and help him to quit. Seeing the presence of significant liver fibrosis on FibroScan®, as well as suboptimal glycaemic levels (HbA_{1c} ≥ 8%, 64 mmol/mol), in addition to lifestyle modifications it is possible to add a second glucose-lowering agent, such as pioglitazone or injectable glucagon-like peptide 1 (GLP-1) receptor agonists (e.g. liraglutide, semaglutide, or dulaglutide). If plasma triglyceride levels remain above 150 mg/dl (>1.8 mmol/l), it would be reasonable to prescribe fenofibrate or omega-3 PUFA supplementation, in addition to lifestyle recommendations. If his blood pressure remains above 140/90 mmHg, it would be reasonable to increase the ramipril dosage to 10 mg/d or add another antihypertensive drug.

Upper gastrointestinal endoscopy (for the purpose of confirming or excluding the presence of oesophageal or gastric varices due to portal hypertension) is necessary in those individuals with established cirrhosis [7]. Long-term surveillance for liver-related complications, including HCC, should be undertaken with liver ultrasonography if cirrhosis is present or in those with advanced fibrosis [7]. The cost-effectiveness of screening for NAFLD in people with type 2 diabetes remains controversial. However, a recent comprehensive cost–utility analysis has shown that the screening for NAFLD in people with type 2 diabetes, based on the use of ultrasonography, serum transaminase levels, and followed by non-invasive testing for advanced fibrosis, is cost-effective compared to not screening [44]. Hence, some authors recommend NAFLD screening for individuals with type 2 diabetes [7, 44]. Table 57.4 shows a typical presentation of a person with coexistent type 2 diabetes and NAFLD.

Aetiology and pathogenesis of non-alcoholic fatty liver disease

The aetiology and pathogenesis of NAFLD are not fully understood. As shown in Table 57.5, several risk factors, including age, sex, ethnicity, lifestyle habits, genetic variants, and multiple acquired metabolic risk factors, can interact additively and potentially synergistically in different ways and contribute to the development and progression of NAFLD [45]. A schematic representation of the putative pathological mechanisms associated with the development and progression of NAFLD is shown in Figure 57.2.

Table 57.5 Main risk factors for non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

Overweight or obesity (body mass index [BMI] ≥25 kg/m^2 in white European individuals; BMI ≥23 kg/m^2 in Asian individuals)
Abdominal obesity (waist circumference ≥94 cm in white European men and ≥80 cm in white European women; ≥90 cm in Asian men and ≥80 cm in Asian women)
Insulin resistance
Pre-diabetes (i.e. impaired fasting glycaemia, impaired glucose tolerance) or established type 2 diabetes
Atherogenic dyslipidaemia
Arterial hypertension
Metabolic syndrome[a]
Family history of type 2 diabetes, NAFLD, or premature cardiovascular disease
NAFLD-related genetic variants, e.g. *PNPLA3* rs738409 C > G, *TM6SF2* rs58542926 C > T, *GCKR* rs1260326 C > T, *GCKR* rs780094 A > G, *MBOAT7* rs641738 C > T

[a] The National Cholesterol Education Program Adult Treatment Panel III diagnostic criteria for the metabolic syndrome include three or more of the following metabolic risk abnormalities: waist circumference >102 cm (men), >88 cm (women); plasma triglycerides ≥150 mg/dl or drug treatment; high-density lipoprotein (HDL) cholesterol <40 mg/dl and <50 mg/dl for men and women, respectively, or drug treatment; blood pressure ≥130/85 mmHg or drug treatment; fasting plasma glucose ≥100 mg/dl, previously diagnosed type 2 diabetes, or use of glucose-lowering agents.
Source: Data from EASL-EASD-EASO 2016 [1] and Chalasani et al. 2018 [2].

Genetic factors predisposing to more severe non-alcoholic fatty liver disease

Numerous genome-wide association studies (GWAS) have clearly identified important genetic contributors to the development and progression of NAFLD [45, 47–49]. Four genetic

variants are noteworthy of mention for several reasons, including their biological plausibility, the relationship with severe NAFLD, and the reproducibility of the findings. Among these four genetic variants, one encodes patatin-like phospholipase domain-containing-3 (PNPLA3) [45, 47–49]. The single-nucleotide polymorphism rs738409 C > G (p.I148M) in *PNPLA3* is defined as a non-synonymous cytosine-to-guanine nucleotide transposition mutation, resulting in an isoleucine-to-methionine amino acid change at codon 148 [45, 47–49]. The wild-type PNPLA3 protein has hydrolase activity on triglycerides and retinyl esters [47–49]. The 148 M substitution determines a loss of function in the enzymatic activity, thereby leading to an entrapment of triglycerides and retinyl esters within lipid droplets in both hepatocytes and hepatic stellate cells [47–49]. Alterations in lipid droplet architecture and in the retinol metabolism of both hepatocytes and hepatic stellate cells play a key role in the development and progression of NAFLD [47–49]. *PNPLA3* rs738409 C > G variant is closely associated with greater susceptibility to NASH, cirrhosis, and HCC [45, 47–49]. Some studies have also reported an association between this genetic variant and liver-related mortality in NAFLD [45, 47–50]. In addition, homozygosity of the *PNPLA3* rs738409 G variant appears to exert its greatest adverse effect on NAFLD severity among individuals in the highest BMI category, while those with a high BMI who are homozygous for the wild-type *PNPLA3* (CC), or who are heterozygous (CG) for this mutation, have a substantially lower risk of NAFLD progression [51].

Another variant that is associated with greater susceptibility to NASH occurs within the transmembrane-6 superfamily member 2 *(TM6SF2)* gene on chromosome 19 [45, 47–49]. The *TM6SF2* rs58542926 C > T (p.E167K) variant is strongly associated with increased hepatic fat content and greater risk of more severe liver disease in NAFLD [45, 47–49, 52]. Mechanistic studies indicate that *TM6SF2* modulates hepatic lipid efflux [45, 47–49]. Deletion (or mutation) of the *TM6SF2* gene results in a reduction in hepatic lipoprotein secretion, as well as an increase in hepatic fat accumulation and hepatocellular lipid droplet size [45, 47–49]. In this context, the *TM6SF2* rs58542926 C > T variant produces a loss of function of the protein [45, 47–49]. Studies have also suggested that *TM6SF2* gene variants may be associated with different disease phenotypes [45, 47–49]. Indeed, evidence now suggests that *TM6SF2* may act as a 'controller', with the *TM6SF2* rs58542926 T allele driving hepatic triglyceride retention and the C allele facilitating very low-density lipoprotein (VLDL) excretion (thus protecting the liver), while at the same time increasing the risk of CVD (i.e. the so-called *TM6SF2* Catch-22 paradigm) [53].

Variants in the genes encoding glucokinase regulator (*GCKR*) and membrane bound O-acyl transferase 7 (*MBOAT7*) also play a role in the development of NAFLD [45, 47–49]. *GCKR* modulates hepatic *de novo* lipogenesis by controlling the influx of glucose in hepatocytes [47–49]. Two genetic variants in the *GCKR* gene locus, rs1260326 C > T and rs780094 A > G, have been associated with NAFLD and its more severe histological forms [47–49]. The most common missense loss-of-function *GCKR* mutation is rs1260326 C > T, which encodes the P446L protein variant [47–49]. The P446L variant adversely affects the capacity of *GCKR* to regulate the glucokinase in response to fructose-6-phosphate, thereby activating hepatic glucose uptake [47–49]. This results in increased malonyl-CoA that induces hepatic *de novo* lipogenesis, inhibits fatty acid oxidation, and promotes hepatic steatosis [47–49].

Membrane-bound O-acyltransferase domain containing 7 (MBOAT7) is a protein involved in the remodelling of phosphatidylinositol with arachidonic acid [47–49]. The *MBOAT7* rs641738 C > T variant is a common genetic variant linked to the downregulation of MBOAT7 mRNA and protein [47–49]. The *MBOAT7* rs641738 C > T variant is associated with decreased levels of phosphatidyl-inositol–containing arachidonic acid in hepatocytes [47–49]. Recently, this genetic variant was found to be associated with a higher risk of NAFLD and advanced fibrosis in adults of European descent [54]. However, genetic variants in *GCKR* and *MBOAT7* produce a smaller effect on the risk of progressive NAFLD compared with *PNPLA3* and *TM6SF2* genetic variants [47]. A general concept based on available genetic studies is that the risk of progressive NAFLD is influenced by the effect of these genetic variants on hepatic fat accumulation, thereby emphasizing that accumulation of lipids in hepatic droplets plays a major role in liver damage [47].

Finally, other genes affecting NAFLD progression, identified by candidate gene analyses, have been validated in large studies or using transmission disequilibrium tests [45, 47–49]. Presently, they include *LPIN1* rs13412852 C > T, *SOD2* rs4880 C > T, *UCP2* rs695366 G > A, *ENPP1* K121Q rs1044498 A > C, *IRS1* rs1801278 A > C, *IL28B* rs12979860 C > T, *KLF6* rs3750861 G > A, *MERTK* rs4374383 G > A, and *FNDC5* rs3480 A > G. All these genetic variants have also been implicated in the hepatic regulation of lipid metabolism, insulin signalling, inflammation, oxidative stress, and fibrogenesis [45, 47–49].

Obesity and insulin resistance

A majority of people with NAFLD have obesity (~50%), atherogenic dyslipidaemia (~69%), or type 2 diabetes (~25%) [55]. Individuals with NASH are more likely to be overweight or obese compared to those with simple steatosis (NAFL) or the general population [55]. In individuals with severe obesity, the prevalence of imaging-defined NAFLD is as high as ~90%, although this percentage varies across published studies according to age, ethnicity, degree of obesity, pre-existing type 2 diabetes, and imaging techniques used for diagnosing NAFLD [56, 57]. Notably, more than 30% of individuals with severe obesity have NASH with varying stages of liver fibrosis identified histologically [58]. It has been demonstrated that weight gain is associated with dysfunction of adipocytes that is closely associated with local inflammation and production of a variety of pro-inflammatory cytokines (e.g. tumour necrosis factor-α [TNF-α] and interleukin-6 [IL-6]), thereby promoting systemic chronic inflammation and insulin resistance (IR) (Figure 57.2) [45, 58, 59]. Insulin resistance alters the capacity of adipocytes to accumulate fat and promotes lipolysis [45, 59]. Hepatocytes take up free fatty acids via fatty acid transport protein-5 (FATP5) and the scavenger receptor CD36 [45, 59]. The accumulation of free fatty acids within the hepatocytes drives the synthesis of triglycerides and impairs hepatic insulin signalling by activating protein kinase Cε (PKCε) [45, 59]. These mechanisms may also promote hepatic gluconeogenesis and chronic hyperglycaemia [45, 59].

Liver metabolism plays a key role in hepatic steatosis by producing lipid from carbohydrates (hepatic *de novo* lipogenesis) (Figure 57.2) [45, 59]. In a study enrolling individuals with metabolic syndrome and/or elevated serum transaminase levels, it has been clearly reported that hepatic *de novo* lipogenesis was around threefold higher in individuals with NAFLD compared to those without NAFLD, thus further supporting a pathogenetic role of *de*

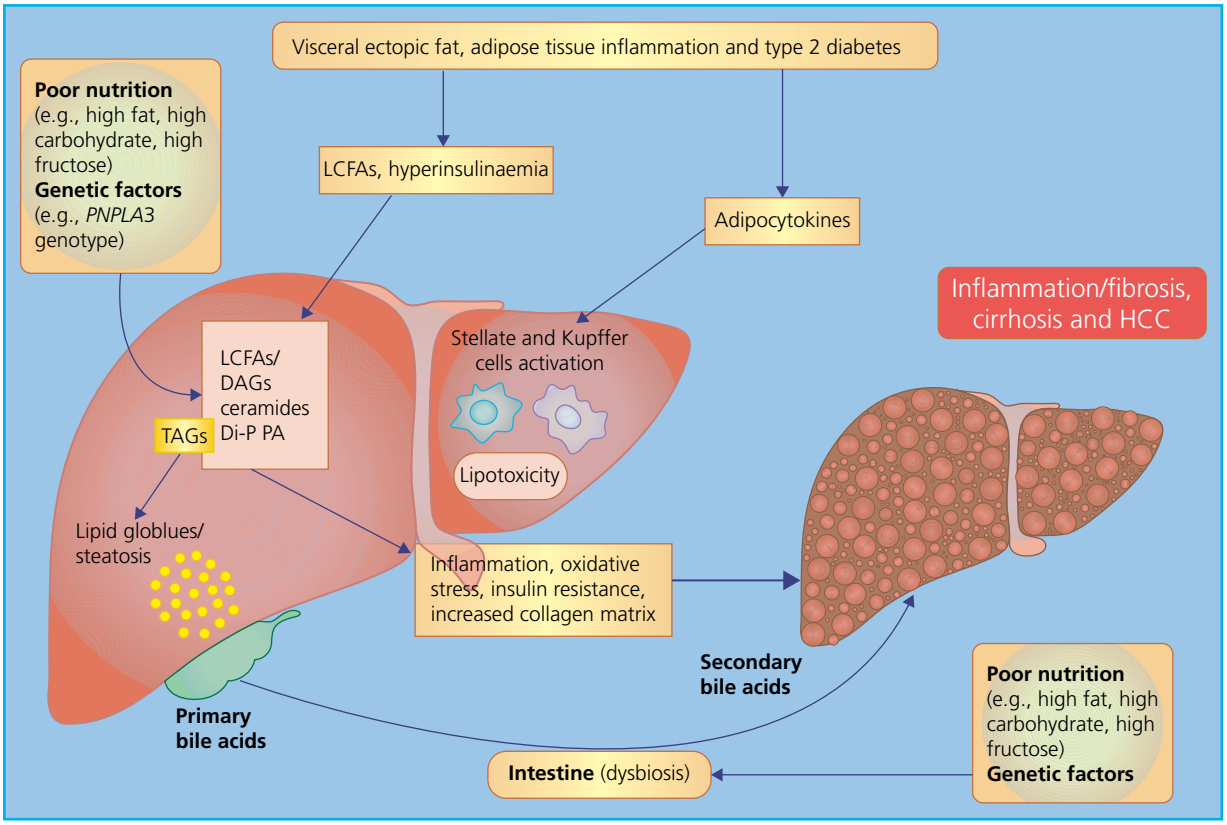

Figure 57.2 Principal pathological mechanisms associated with the development and progression of non-alcoholic fatty liver disease (NAFLD). Visceral ectopic fat accumulation, adipose tissue inflammation, and type 2 diabetes promote the development and progression of NAFLD. Western diet (especially high fat and high fructose intakes), along with some common genetic variants (e.g. *PNPLA3* polymorphism), play a role in NAFLD progression, increasing hepatic lipid accumulation and promoting liver fibrosis. Intestinal dysbiosis (defined by the presence of perturbations to the structure of complex commensal communities in the intestinal microbiota) alters the production of short-chain fatty acids (from fermentation of dietary carbohydrate) and promotes the production of lipopolysaccharide into the portal circulation. These factors then promote a pro-inflammatory hepatic stimulus, increasing the risk of NAFLD progression. See text for further details. DAG, di-acylglycerol; HCC, hepatocellular carcinoma; LCFAs, long-chain fatty acids; Di-P PA, Di-palmitoyl phosphatic acid; *PNPLA3*, patatin-like phospholipase domain-containing 3. Source: Reproduced by permission from Byrne et al. 2015 [46].

novo lipogenesis in hepatic steatosis [60]. Through the activity of two main transcription factors, sterol regulatory element-binding protein 1 (SREBP1) and carbohydrate-responsive element-binding protein (ChREBP), both insulin and glucose may upregulate the enzymes implicated in hepatic *de novo* lipogenesis, thereby inducing hepatic fat accumulation [45, 59]. Diets high in fats and carbohydrates also provide substrates for hepatic fat synthesis and contribute to the development of hepatic steatosis via increased *de novo* lipogenesis [45, 59]. Moreover, dietary fructose intake may increase hepatic *de novo* lipogenesis and visceral adiposity, and induce insulin resistance [45, 59].

All forms of NAFLD are closely linked with systemic and hepatic insulin resistance (Figure 57.2) [45, 59]. In the liver, insulin resistance is characterized by impaired insulin-mediated suppression of hepatic glucose production, increased gluconeogenesis, and decreased glycogen synthesis [45, 59]. Insulin activates its receptor, which results in tyrosine phosphorylation of insulin receptor substrate (IRS) and activation of downstream effector pathways, such as the phosphatidylinositol 3-kinase (PI3K)-phosphoinositide-dependent kinase-protein kinase B (AKT) and the RAS-extracellular-signal regulated kinase (ERK) pathways [45, 59]. Several pro-inflammatory pathways can interfere with insulin signalling by inhibiting phosphorylation of IRS [45, 59]. The inhibitor of NFκB kinase β (IKKβ) is an important stimulus for insulin resistance, along with its role as NFκB activator [45, 59]. Experimental data suggest that activation of NFκB and downstream inflammatory signalling pathways play a key role in the development of hepatic insulin resistance [45, 59]. Although there is a link between NAFLD and insulin resistance, observational and GWAS studies have identified some genetic variants (e.g. *PNPLA3* and *TM6SF2* variants) that are associated with greater NAFLD severity, but not with greater insulin resistance [45, 59, 61].

Triglycerides *per se* are not hepatotoxic products [45, 59]. Rather, precursors of triglyceride (i.e. free fatty acids and diacylglycerols) may induce hepatic lipotoxicity [45, 59]. Lipotoxicity drives the release of multiple pro-inflammatory mediators, leading to hepatocyte death [45, 59]. Dying hepatocytes can promote the release of several other factors that, in turn, may activate healing responses in hepatocytes [45, 59]. These healing responses are typically characterized by three elements: recruitment of other cell types (myofibroblasts); remodelling of the vasculature; and recruitment of immune cells that can further release multiple factors able to amplify liver injury [45, 59].

As shown in Figure 57.2, other putative mechanisms implicated in the development and progression of NAFLD include changes in gut microbiota, bile acids and their metabolites, and products of choline metabolism influenced by the intestinal microbiota.

Non-alcoholic fatty liver disease as a multisystem disease

Several studies have consistently documented that NAFLD is associated with an increased risk of extrahepatic complications, such as CVD (which is the leading cause of mortality in people with NAFLD), type 2 diabetes, chronic kidney disease (CKD), and certain types of extrahepatic cancers (especially colorectal cancers) [5–8, 39, 46, 62] (Figure 57.3).

Risk of type 2 diabetes

Type 2 diabetes is associated with increased risk of hospital admission or death for all common chronic liver diseases and the strength of the association may vary by type of chronic liver disease, sex, and socioeconomic status [63]. NAFLD is also associated with an increased risk of CVD, cancer, and mortality among people with type 2 diabetes [64]. Moreover, individuals with NAFLD have an increased risk of developing type 2 diabetes compared to those without NAFLD, even after adjustment for common metabolic risk factors [46, 65–67]. A comprehensive meta-analysis of 33 longitudinal cohort studies (involving 501 022 middle-aged individuals) showed that NAFLD was significantly and independently associated with a 2.2-fold increased risk of incident diabetes over a median follow-up period of five years [68]. Notably, this risk increased further with the severity of NAFLD (especially the severity of liver fibrosis) [68]. In this context, in a small retrospective study of Swedish people with biopsy-proven NAFLD, the authors showed that a significantly higher proportion of individuals with histologic fibrosis stages F3–4 developed incident type 2 diabetes, when compared to those with fibrosis stages F0–2 (51% vs 31%), over a mean follow-up of 18 years [69].

Some observational studies have also investigated the risk of incident type 2 diabetes in relation to changes in NAFLD status over time. In a retrospective cohort study of ~13 000 Korean individuals who were followed for at least five years, improvement in hepatic steatosis (on ultrasonography) over time was associated with a decreased risk of incident type 2 diabetes, independent of temporal changes in body weight [70], suggesting that liver fat *per se*, or factors associated with a change in liver lipid, may directly influence the risk of incident type 2 diabetes. In line with these findings, another large Korean study reported that improvement of NAFLD (mostly based on FLI scores) could reduce the risk of incident type 2 diabetes, while the development of new NAFLD could increase the risk of type 2 diabetes [71].

The underlying mechanisms by which NAFLD modifies the risk of incident type 2 diabetes are not fully understood [5, 59, 68]. However, NAFLD, especially NASH with varying amounts of liver fibrosis, exacerbates systemic and hepatic insulin resistance and induces the release of many pro-inflammatory cytokines, hepatokines, and other "diabetogenic" mediators that may actively contribute to the development of type 2 diabetes [5, 59, 68, 72]. Conversely, dysfunction of adipose tissue with excessive lipolysis and diets high in fats and carbohydrates supply the liver with chylomicron remnants and free fatty acids [5, 59, 68]. Elevated hepatic lipid availability, along with inadequate adaptation of mitochondrial function, results in the hepatic production of diacylglycerols and various metabolites (e.g. ceramides) that further promote NAFLD development and progression [5, 59, 68].

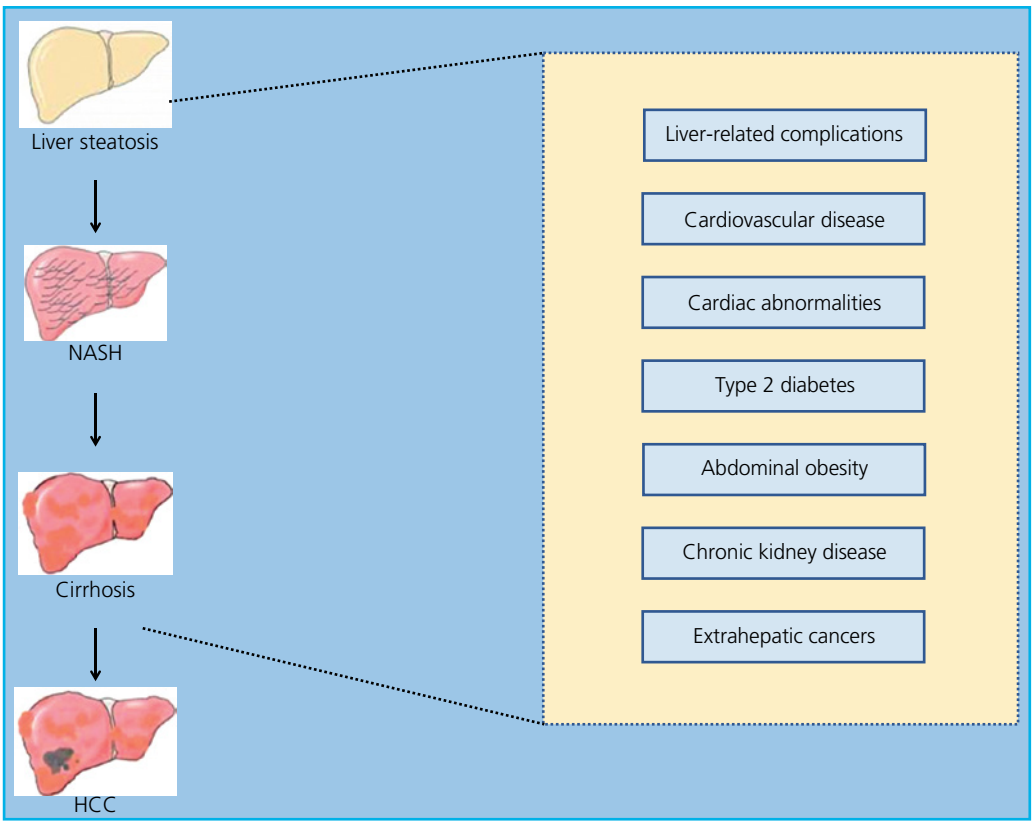

Figure 57.3 Principal liver-related and extrahepatic complications associated with non-alcoholic fatty liver disease. HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis.
Source: Modified by permission from Mantovani et al. 2020 [5].

Worsening of glycaemic levels in individuals with type 2 diabetes and non-alcoholic fatty liver disease

Coexistence of NAFLD in people with type 2 diabetes has been associated with higher glycated haemoglobin (HbA_{1c}) and greater hepatic and peripheral insulin resistance [7, 59, 73–76]. The hepatic fat content appears to be the main factor explaining the daily amount of insulin required to achieve optimal glycaemic management in individuals with insulin-treated type 2 diabetes [73]. In an elegant small study of individuals with insulin-treated type 2 diabetes and HbA_{1c}, hepatic fat content (measured by MRS) was strongly associated with the daily insulin dose and the ability of insulin to suppress hepatic glucose production during hyperinsulinaemic–euglycaemic clamp, explaining at least in part the inter-individual variation in insulin requirements [74]. This result was confirmed by another study showing that individuals with NAFLD (assessed by FibroScan® with CAP) were more likely to have features of the metabolic syndrome, elevated HbA_{1c}, and greater requirement for insulin treatment compared to those without NAFLD [76].

Risk of worsening fibrosis and cirrhosis in individuals with type 2 diabetes

Strong evidence shows that individuals with overt type 2 diabetes are at a consistently higher risk of developing NASH and advanced fibrosis, as well as a greater risk of serious liver-related complications, including cirrhosis, liver failure, and HCC [2, 4, 5, 7, 8, 77]. In addition to the findings from the NASH-Clinical Research Network cohort study [27], a large administrative health database (including nearly 2.5 million Canadian individuals) documented that individuals with newly diagnosed type 2 diabetes had a ~2-fold increased risk of developing cirrhosis, liver failure, or liver transplantation compared with matched individuals without type 2 diabetes, during a follow-up of 12 years [78]. Using an electronic administrative database of death certificates in Northern Italy, the authors showed that people with type 2 diabetes had a ~3-fold higher risk of dying of chronic liver diseases, mainly due to NAFLD [79].

Once chronic liver disease progresses to end-stage liver disease, the presence of type 2 diabetes is a strong predictor of worse clinical outcomes [80, 81]. Type 2 diabetes is also closely associated with the severity of liver disease (cirrhosis) based on the Child-Pugh class and the model for end-stage liver disease (MELD) score [80, 81]. In addition, type 2 diabetes is associated with more severe hepatic encephalopathy among individuals with established cirrhosis, regardless of the severity of liver disease and its aetiology [80]. The incidence of HCC and HCC-specific mortality is higher in people with type 2 diabetes than in those without [81]. In a meta-analysis of 28 prospective studies, it has been confirmed that compared to those without type 2 diabetes, individuals with type 2 diabetes had a ~2-fold increased risk of incident HCC and HCC-specific mortality [82]. Furthermore, individuals with type 2 diabetes and HCC also had a ~40% increased risk of all-cause mortality and a ~90% increased risk of decompensated cirrhosis [82].

The effect of type 2 diabetes on the risk of HCC seems to be even more relevant in individuals carrying the *PNPLA3* rs738409 polymorphism [81]. In a case–control study enrolling 257 individuals with HCC and 494 controls, the risk of HCC was higher in individuals with type 2 diabetes carrying the *PNPLA3* rs738409 variant than in people without diabetes with the same genetic variant [83]. In this context, the presence of insulin resistance and compensatory hyperinsulinaemia plays a key role in HCC development in type 2 diabetes, promoting growth signalling pathways, pro-inflammatory cytokine production, and neoangiogenesis [81, 84].

Collectively, these findings strongly emphasize that clinicians need to be aware of the possible coexistence of NAFLD in individuals with type 2 diabetes, and, when a diagnosis of NAFLD is made, clinicians should determine whether NASH with advanced fibrosis is also present.

Risk of cardiovascular disease, arrhythmias, and cardiac diseases

As previously reported, the leading cause of mortality among NAFLD individuals is CVD [5, 6, 39, 85]. In a meta-analysis of 45 observational studies including >8 million people followed from 4 to 13 years, the pooled CVD-specific mortality rate in individuals with NAFLD (irrespective of type 2 diabetes status) was approximately 5 per 1000 person-years [3]. Using the National Vital Statistics System multiple-cause mortality data (2007–2016), Paik et al. showed that CVD was one of the most important causes of mortality among US individuals with NAFLD [85]. Several hospital-based and population-based cohort studies have shown that people with NAFLD have an increased risk of fatal and non-fatal CVD events, when compared with those without NAFLD, even after adjusting for many traditional CVD risk factors, in individuals both with and without type 2 diabetes [6–8, 39, 73, 86, 87]. A 2016 meta-analysis of 16 observational studies (involving 34 043 individuals) confirmed that individuals with NAFLD had a 64% higher risk of fatal and/or non-fatal CVD events than those without NAFLD over a median period of 6.9 years [86]. Individuals with more 'severe' NAFLD were also more likely to develop fatal and non-fatal CVD events (random-effects odds ratio 2.58, 95% confidence interval [CI] 1.78 to 3.75) [86]. Other studies confirmed that the magnitude of risk of CVD events paralleled the underlying severity of NAFLD [41, 88, 89]. More recently, in a nationwide, matched-cohort study of 10 568 Swedish individuals with biopsy-confirmed NAFLD and 49 925 matched controls (followed up for a median period of 14.2 years), the investigators reported that all NAFLD histological stages were independently associated with increased mortality rates from CVD [41]. In a multinational retrospective cohort study of 619 individuals with biopsy-proven NAFLD (38% with type 2 diabetes), increasing fibrosis stage, but no other histological features of NASH, was strongly associated with long-term overall mortality, liver transplantation, and liver-related complications [88]. Similar findings were also documented in other hospital-based cohorts involving people with type 2 diabetes [6, 8, 26, 39, 73, 87].

To date, increasing clinical evidence substantiates the existence of a strong relationship of NAFLD with subclinical myocardial remodelling and dysfunction, valvular heart diseases (mainly aortic valve sclerosis and mitral annulus calcification), and arrhythmias (mainly permanent atrial fibrillation) in individuals with and without type 2 diabetes [6, 8, 26, 39, 46, 73, 87]. For example, in a cross-sectional study enrolling individuals with type 2 diabetes, Mantovani et al. reported that NAFLD (on ultrasonography) was independently associated with increased risk of early left ventricular diastolic dysfunction [90]. Another cross-sectional study showed that cardiac structure alterations (assessed by cardiac magnetic resonance) were more prevalent in individuals with type 2 diabetes and NAFLD compared to those with NAFLD alone or people without either condition [91]. Some studies using liver biopsy

or FibroScan® reported a graded, positive relationship between cardiac structure abnormalities and the severity of NAFLD in individuals with and without type 2 diabetes [39]. Studies have also reported an association between NAFLD and risk of aortic valve sclerosis and mitral annulus calcification in individuals with and without type 2 diabetes [39, 92].

Accumulating clinical evidence now suggests that NAFLD is associated with an increased risk of permanent AF in individuals with and without type 2 diabetes [39]. AF is the most common sustained arrhythmia in clinical practice, and it is closely related to cardiovascular morbidity and mortality [39]. A large meta-analysis of five observational studies (involving a total of ~240 000 middle-aged and elderly individuals) showed that NAFLD was associated with a higher prevalence and incidence of permanent atrial fibrillation [93]. In a retrospective study of individuals undergoing atrial fibrillation ablation, it has been reported that NAFLD was associated with increased arrhythmia recurrence rates following ablation, during a mean follow-up of ~2.5 years [94]. Other studies documented that imaging-defined NAFLD was associated with an increased risk of prolonged QTc interval, ventricular arrhythmias, or certain cardiac conduction defects in people with type 2 diabetes [39, 95–98], even after adjustment for established CVD risk factors. The aforementioned findings are of clinical importance because these NAFLD-related cardiac and arrhythmic complications may, at least in part, contribute to the increased risk of CVD events observed among individuals with NAFLD.

There are most likely multiple underlying mechanisms through which NAFLD may directly increase the risk of CVD and cardiac and arrhythmic complications [46]. Although NAFLD might be simply a consequence or a marker of shared cardio-metabolic risk factors and comorbidities, growing evidence supports the notion that NAFLD plays a part in the pathophysiology of CVD and other cardiac and arrhythmic complications (Figure 57.4).

Current evidence indicates that a diagnosis of NAFLD identifies a subgroup of individuals that are at high risk of CVD mortality and morbidity, and the EASL-EASO-EASD and AASLD practice guidelines strongly recommend a CVD risk assessment in all individuals with NAFLD [1, 2].

Risk of microvascular complications

Several studies have reported that NAFLD is associated with an increased risk of CKD in people with and without type 2 diabetes, independent of established cardio-renal risk factors [62]. In 2008, the Valpolicella Heart Diabetes Study showed for the first time that individuals with type 2 diabetes and NAFLD (on ultrasonography) had

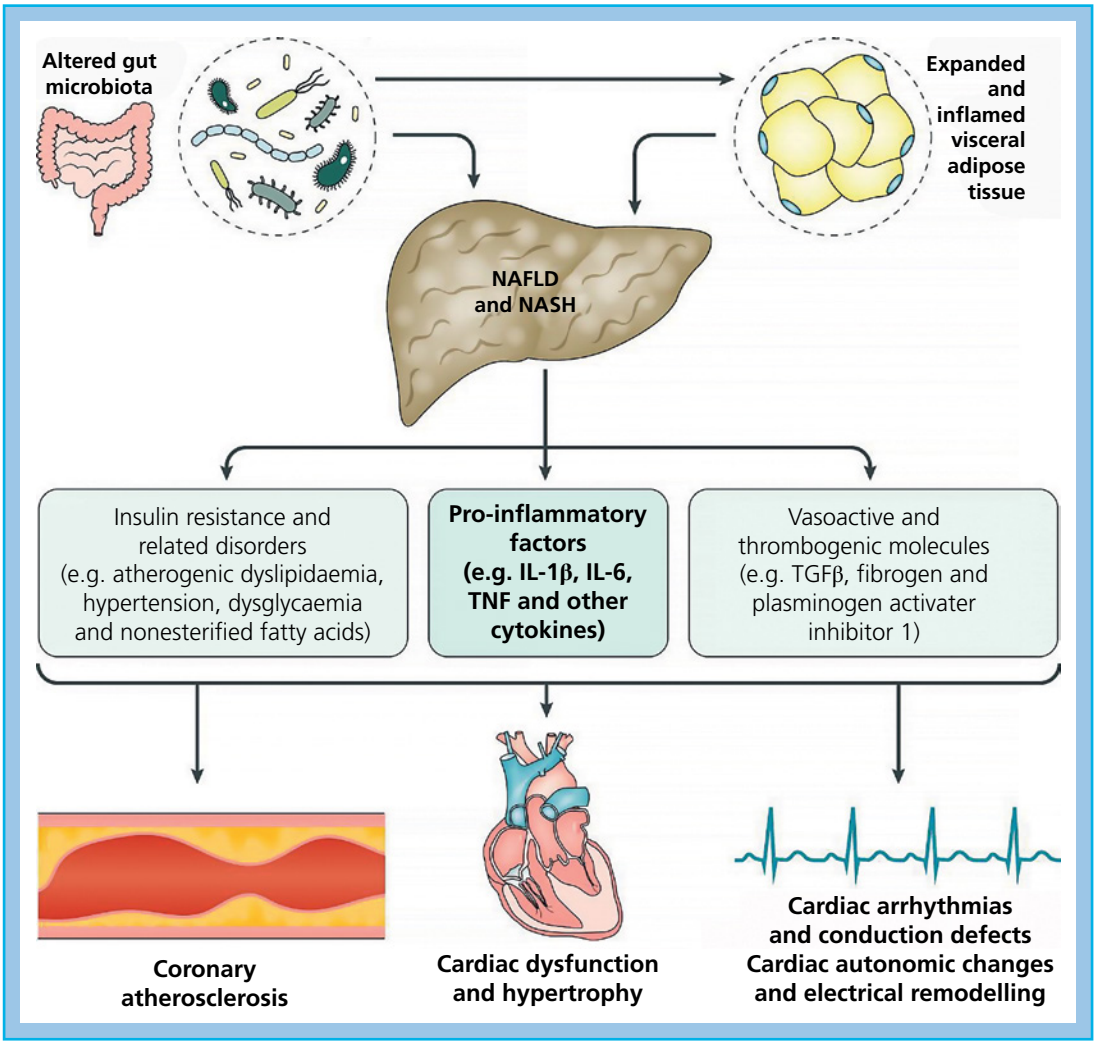

Figure 57.4 Possible biological mechanisms responsible for the association between non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) the risk of developing cardiovascular disease (CVD) and other structural cardiac complications. NAFLD may directly promote the development and progression of CVD complications, possibly through the hepatic production of lipids and atherogenic lipoproteins; the induction of hepatic/peripheral insulin resistance and dysglycaemia; as well as the release of numerous pro-inflammatory, pro-fibrogenic, and pro-coagulant mediators into the bloodstream. See text for further details. IL, interleukin; TGF, tumour growth factor; TNF, tumour necrosis factor. Source: Reproduced by permission from Anstee QM 2018 [39].

an increased risk of incident CKD stage ≥3, compared to their counterparts without NAFLD, over a mean follow-up of 6.5 years [99].

A large meta-analysis of 13 observational longitudinal studies involving more than 1 million middle-aged individuals from different countries showed that the long-term risk of developing CKD stage ≥3 was increased ~1.5-fold in individuals with NAFLD. Furthermore, the risk of incident CKD stage ≥3 remained significant in those studies where analysis was adjusted for age, sex, adiposity measures, smoking, pre-existing type 2 diabetes, hypertension, dyslipidaemia, and baseline estimated glomerular filtration rate (eGFR). In addition, this risk seemed to parallel the severity of NAFLD, especially the severity of liver fibrosis [100]. Another meta-analysis showed that this risk could be even greater in individuals with type 2 diabetes [101].

Experimental and clinical data suggest that NAFLD may contribute to the activation of multiple pathways potentially involved in CKD pathophysiology (Figure 57.5) [46, 62, 102]. For example, impaired activation of the renin–angiotensin system may contribute to the reno-vascular injury by inflammation and coagulation pathways. Atherogenic dyslipidaemia, insulin resistance, increased oxidative stress, and pro-inflammatory factors that are promoted by NAFLD may all contribute to the development of vascular and renal damage. Increased production of toxins by intestinal microbiota may induce renal injury or worsen the liver damage. Finally, preliminary evidence suggests an association between the *PNPLA3* rs738409 variant and the presence of kidney dysfunction, independent of common renal risk factors and NAFLD severity [62, 102–108].

Treatment for non-alcoholic fatty liver disease in individuals with type 2 diabetes

The EASL-EASO-EASD guidelines recommend consideration of pharmacological treatment for NAFLD not only in those with NASH with varying stages of liver fibrosis, but also in individuals with less severe liver disease who are at the highest risk for disease progression (e.g. those with type 2 diabetes or metabolic syndrome) [1]. Conversely, the AASLD [2] and the UK National Institute for Health and Care Excellence (NICE) guidelines [109] recommend limiting pharmacological treatment for the liver disease only to those with biopsy-proven NASH and varying stages of fibrosis.

Currently, there are no licensed pharmacological treatments specifically for liver disease in NAFLD [1, 2]. The management of NAFLD is based on the following main principles:

- To promote weight loss by diet and exercise (Table 57.6).
- To control all coexisting cardiometabolic risk factors.
- To prevent the development and progression of both liver-related and extrahepatic complications [1, 2].

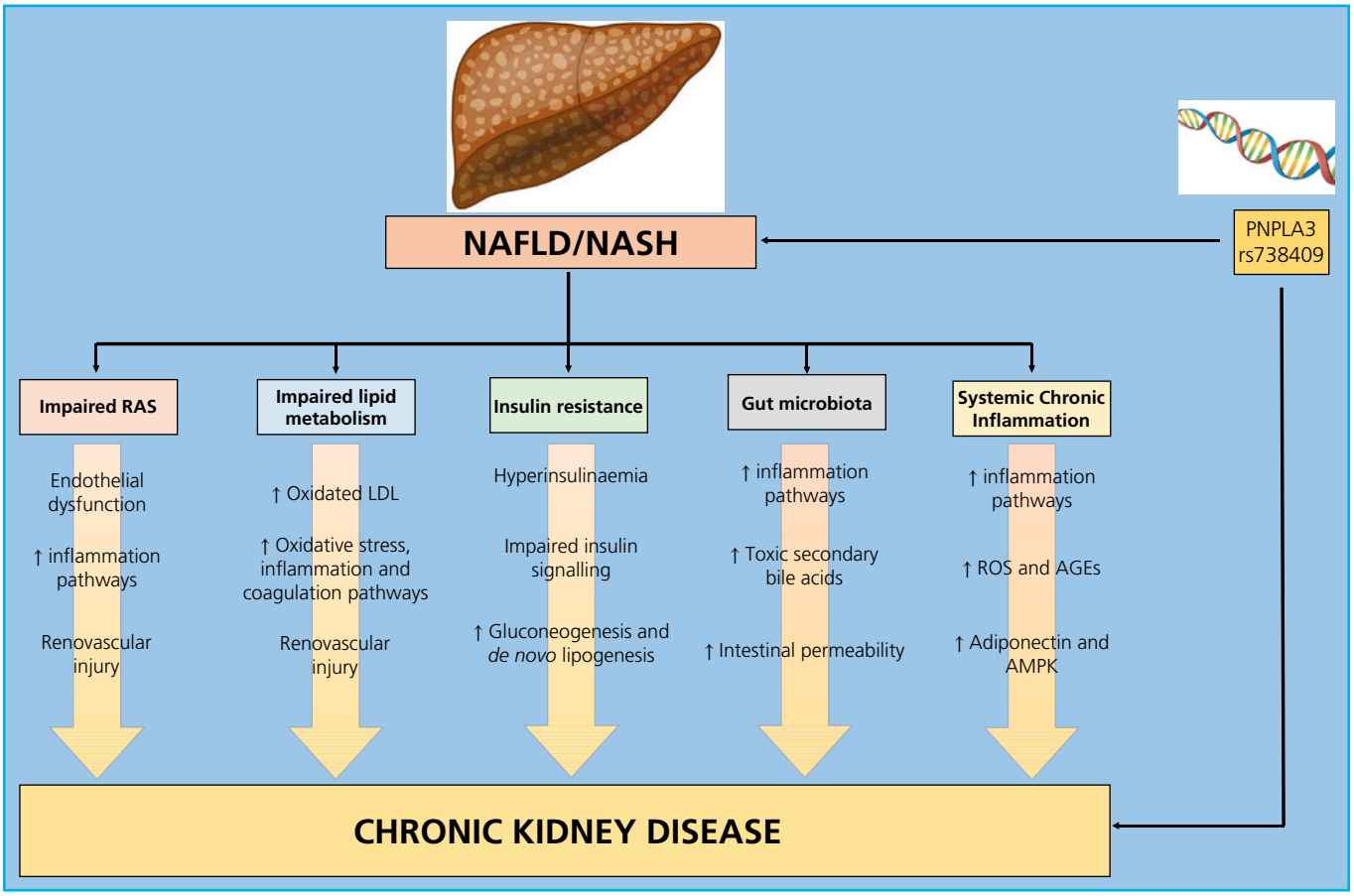

Figure 57.5 Putative biological mechanisms by which non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) may contribute to the development and progression of chronic kidney disease. See text for further details. AGEs, advanced glycation end-products; AMPK, adenosine monophosphate-activated protein kinase; LDL, low-density lipoprotein; NASH, non-alcoholic steatohepatitis; *PNPLA3*, patatin-like phospholipase domain-containing protein-3; RAS, renin–angiotensin system; ROS, reactive oxygen species. Source: Reproduced by permission from Mantovani et al. [102].

Table 57.6 Recommended lifestyle interventions to improve non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) liver histology.

Nutrition
5–10% weight loss as target
Long-term maintenance approach
Prefer Mediterranean diet (i.e. high intake of vegetables, legumes, whole grains, olive oil, fish, seafood, nuts, and fruits, as well as low intake of red meat, processed meats, and sweets)
Avoid alcohol intake
Avoid fructose intake, soft drinks, processed meat, and saturated fatty acids
Low-carbohydrate ketogenic diets
Physical activity
Moderate-intensity aerobic physical activities (~150 min/wk)
Resistance training (alternatively to aerobic physical activities)
3–5 sessions weekly
Other
Avoid cigarette smoking

Lifestyle modifications

Strong evidence supports the role of lifestyle modifications as primary therapy for management of NAFLD [1, 2, 110]. Weight loss can result in improvement or resolution of NAFLD and decrease in risk of CVD and type 2 diabetes [110]. Weight reduction of ≥10% promotes histological resolution of NASH, as well as fibrosis improvement by at least one stage [110]. Mild to moderate weight loss (5–10%) may improve hepatic steatosis, necro-inflammation, but not liver fibrosis [110]. The EASL-EASO-EASD and AASLD guidelines for NAFLD management indicate that 5–10% weight loss should be the goal of lifestyle interventions in most individuals with overweight or obesity and NAFLD [1, 2]. Some evidence suggests that individuals without obesity can also achieve NAFLD resolution or improvement with modest weight loss of 3–10%, and that they are more likely to maintain weight reduction and normal serum liver enzyme levels over time than individuals with obesity and NAFLD [111].

The effect of weight loss on the histological improvement or resolution of NASH largely reflects the amount of weight reduction, rather than the methods used to achieve it [110]. Different lifestyle interventions (hypocaloric diet, physical exercise) and weight loss induced by drugs or bariatric surgery produced similar favourable effects on NASH resolution and fibrosis regression [110]. All individuals with NAFLD should avoid alcohol consumption [1, 2, 112] and, when possible, the use of hepatotoxic drugs [1, 2]. Healthcare professionals should also recommend avoidance of cigarette smoking, as well as fructose-containing beverages and foods [1, 2].

Different diets have been tested in individuals with NAFLD [110, 113]. Observational studies and small randomized controlled trials (RCTs) have documented that the Mediterranean diet may exert favourable hepatic effects, as this style of food consumption reduces liver fat content and improves the histological severity of NAFLD, regardless of weight loss. Hence, the Mediterranean diet is the most frequently recommended style of eating in people with NAFLD [1, 2, 113]. Importantly, it is well documented that Mediterranean diet also reduces the risk of CVD and type 2 diabetes [113]. Conversely, the consumption of components characterizing a Western dietary pattern has detrimental effects on NAFLD [110, 113]. Potential mechanisms for the hepatic benefits of the Mediterranean diet include the presence of polyphenols, carotenoids, oleic acid, polyunsaturated fatty acids (PUFAs), and fibre [113]. These components favourably influence multiple pathways involving the liver, adipose tissue, and intestine, thereby mediating long-term beneficial effects on NAFLD [114].

Different forms of exercise (aerobic exercise, resistance exercise, or high-intensity intermittent exercise) seem to have similar effects on liver fat content [110, 115]. In a systematic review, physical exercise, irrespective of weight loss, produced a ~20–30% relative reduction in hepatic fat content, as measured by MRS [116]. However, if individuals do not continue to exercise, the benefits are lost [110]. The mechanisms underpinning the changes in liver fat content mediated by exercise may be due to changes in energy balance and improvements in systemic and hepatic insulin resistance and glycaemic management [110]. Exercise also has positive effects on intra-abdominal visceral accumulation and hepatic fatty acid uptake, with an increase in VLDL clearance, further promoting liver fat reduction [110]. Lastly, given that people with NAFLD are at high CVD risk, it is important to remember that the beneficial effects of exercise extend beyond the liver, with favourable effects on traditional CVD risk factors [110]. Table 57.6 summarizes the main lifestyle interventions that may improve the histology of NAFLD/NASH, as recommended by EASL-EASO-EASD and AASLD practice guidelines [1, 2].

Bariatric surgery

The most widely adopted bariatric surgery procedures are laparoscopic sleeve gastrectomy, laparoscopic Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding, and duodenal switch [117]. Bariatric surgery may substantially improve all of the histological features of NAFLD, including liver fibrosis [1, 2, 117]. In a meta-analysis of 32 cohort studies comprising 3093 biopsy specimens, bariatric surgery resulted in histological resolution of hepatic steatosis in ~70% of cases, hepatic inflammation in ~50%, ballooning degeneration in ~75%, and hepatic fibrosis in ~40% [118]. However, these beneficial hepatic effects seem to be not always consistent, as a subset of these individuals may progress to more severe forms of NAFLD after bariatric surgery, whereas others may develop *de novo* NAFLD. Specifically, in the aforementioned meta-analysis, the authors found that ~10% of individuals had new or worsening features of NAFLD after bariatric surgery [118].

The possible liver-related benefits derived from bariatric surgery may extend beyond weight loss [45, 119]. Bariatric surgery can increase circulating glucagon-like peptide 1 (GLP-1) levels, which, in turn, decrease appetite, slow gastric emptying, and improve insulin sensitivity and glycaemic management [45]. GLP-1 also modulates bile acid signalling via the farnesoid X receptor (FXR) nuclear receptor, which may modify the gut microbiome [120, 121]. The current guidelines indicate that bariatric surgery could be a therapeutic option in people with type 2 diabetes and severe obesity (i.e. BMI >35 kg/m^2) [1, 2]. Bariatric surgery should also be considered as an alternative option in individuals with obesity and a BMI between 30 and 35 kg/m^2 when type 2 diabetes is not adequately managed by optimal medical regimens, or in the presence of multiple CVD risk factors [1, 2]. Although bariatric surgery is effective, there are some important limitations that should be considered, such as peri–/post-procedural complications, patient acceptability, service availability, and cost [117].

Metformin

Metformin is recommended as the initial drug of choice for people with type 2 diabetes [122, 123]. This drug reduces blood glucose levels mainly through mechanisms involving the AMP-activated protein kinase–dependent reduction in hepatic glucose production and improvement in skeletal muscle glucose uptake [122]. Metformin may also reduce the risk of CVD events and mortality in people with type 2 diabetes, especially in those who have overweight or obesity [122, 123]. In published RCTs involving individuals with biopsy-proven NASH, despite its beneficial effects on serum liver enzyme levels and glycaemic management, metformin showed little or no effects on the resolution of NASH and individual histological scores of NASH (Table 57.7) [124, 125]. Presently, the EASL-EASO-EASD and AASLD practice guidelines for NAFLD management do not recommend metformin for treatment of NAFLD or NASH [1, 2]. As suggested by some observational studies, metformin use is associated with reduced risk of cirrhosis and HCC [126–130]. However, future large RCTs are needed to confirm these findings.

Peroxisome proliferator-activated receptor-γ agonists

Pioglitazone is a selective ligand of the peroxisome proliferator-activated receptor (PPAR)-γ [122, 123]. PPARs are nuclear receptors capable of modulating key elements of glucose and lipid metabolism and also regulate inflammatory and fibrotic processes [131]. By binding PPAR-γ, pioglitazone modulates insulin action, glucose, and lipid metabolism, as well as inflammation and adipose tissue biology [122, 123, 131]. The PPAR-γ2 receptor (one of the three isoforms of PPAR-γ) is highly expressed in adipose tissue, playing a key role in the redistribution of intra-abdominal and subcutaneous adipose tissue by promoting accumulation of triglycerides in peripheral adipose tissue depots [122, 123]. The PPAR-γ receptor is also expressed in Kupffer cells, which are involved in hepatic fibrogenesis [122, 123]. A systematic review showed that the long-term use of pioglitazone in individuals with biopsy-confirmed NASH has significant benefits on serum liver enzyme levels, liver fat content, and resolution of NASH in individuals both with and without type 2 diabetes (Table 57.7) [124].

The effect of pioglitazone on liver fibrosis is rather modest [124]. However, in a placebo-controlled RCT of 101 individuals with biopsy-proven NASH and pre-diabetes or overt type 2 diabetes, who were randomly assigned to pioglitazone (45 mg/d) or placebo for 18 months, Cusi et al. showed that treatment with pioglitazone was associated with greater resolution of NASH and improvement in individual histological scores, including the fibrosis score, compared with placebo [132]. In a meta-analysis of eight RCTs enrolling nearly 500 individuals with biopsy-confirmed NASH who were followed up to 24 months, pioglitazone treatment improved advanced fibrosis in individuals with NASH, irrespective of type 2 diabetes status [133]. Currently, the EASL-EASO-EASD and AASLD practice guidelines for NAFLD management strongly recommend the use of pioglitazone in individuals with biopsy-proven NASH, regardless of the presence or absence of type 2 diabetes [1, 2]. However, it is important to note that pioglitazone is not licensed by most national medicines agencies specifically for treatment of NASH and, for these reasons, its off-label use for NAFLD/NASH treatment requires the patient's informed consent [123]. Concerns regarding weight gain (most trials reported a weight gain of ~2–3 kg after 6–36 months of treatment), peripheral oedema, and risk of distal bone fractures (mostly in postmenopausal women) restrict the use of pioglitazone in many individuals with NASH (Table 57.7).

Table 57.7 Efficacy and safety of main glucose-lowering agents to non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH) treatment.

	Serum liver enzymes	Liver fat content[a]	Liver inflammation[b]	Liver fibrosis[b]	NASH resolution[b]	Common adverse effects
Metformin	↑	↑	=	=	=	Lactic acidosis, diarrhoea, nausea, vomiting, flatulence
Pioglitazone	↑	↑	↑	↑	↑	Moderate weight gain (2–4% of body weight, especially subcutaneous fat), fluid retention, distal bone fractures (mostly in women), bladder cancer (uncertain)
Glucagon-like peptide 1 (GLP-1) receptor agonists (liraglutide, exenatide, dulaglutide, semaglutide)	↑	↑	↑	=	↑[d]	Loss of appetite, nausea, constipation, diarrhoea
Sodium–glucose cotransporter 2 (SGLT-2) inhibitors (empagliflozin, dapaglifozin, canaglifozin)	↑	↑	Unknown[c]	Unknown[c]	Unknown[c]	Genitourinary infections (mainly mycotic infections), diabetic ketoacidosis, hypotension

↑ improved; = no effect; ↓ worse.

NB: Presently, no robust data exist with histological endpoints as a primary outcome to examine the effectiveness of the use of dipeptidyl peptidase 4 (DPP-4) inhibitors for treatment of NAFLD. In addition, DPP-4 inhibitors have a neutral effect on cardiovascular disease outcomes in persons with type 2 diabetes, making this class of glucose-lowering agents less attractive for treatment of NAFLD or NASH [124].

[a] Data derived from randomized controlled trials (RCTs) where liver fat was assessed by imaging techniques.

[b] Data derived from RCTs where liver inflammation, fibrosis, and resolution of NASH were assessed by liver biopsy.

[c] No RCTs with paired liver biopsy data.

[d] RCTs with paired liver biopsy data available only for liraglutide or semaglutide.

Lastly, pioglitazone can exert significant cardiovascular benefits, decreasing the risk of myocardial infarction and stroke in individuals with type 2 diabetes or pre-diabetes [134–136].

New drugs able to promote the safe disposal of various metabolic substrates are under study, especially PPARα/δ and PPARα/γ agonists [131, 137]. Furthermore, a recent phase 2b RCT of 247 people with biopsy-proven NASH (42% with type 2 diabetes) showed that a 24-week treatment with lanifibranor (a pan PPAR agonist) induced significant improvements in resolution of NASH and regression of liver fibrosis compared with placebo [138].

Glucagon-like peptide 1 receptor agonists

GLP-1 receptor agonists (GLP-1 RAs) are a class of glucose-lowering drugs that are able to induce significant weight loss (on average 3–5 kg) and improve insulin resistance [122, 123]. GLP-1 receptors have been documented in human hepatocytes and the activation of such receptors may promote the reduction of hepatic steatosis by improving insulin-signalling pathways [124]. For these reasons, GLP-1 RAs have also been investigated as a therapeutic option for NASH. A recent systematic review supports the use of GLP-1 RAs (mainly liraglutide) to reduce serum aminotransferase levels and improve hepatic steatosis, as detected by imaging techniques or histology (Table 57.7) [124]. Liraglutide was evaluated in individuals with either biochemistry-based or imaging-defined NAFLD by the Liraglutide Effect and Action in Diabetes (LEAD) programme and LEAD-2 study [139], as well as in individuals with biopsy-proven NASH by the Liraglutide Efficacy and Action in NASH (LEAN) trial [140]. Evidence from these and other RCTs documented that liraglutide improved serum liver enzyme levels and induced significant improvements in histological resolution of NASH, hepatic steatosis, and hepatocyte ballooning (Table 57.7). In these RCTs, liraglutide was generally well tolerated and had a similar adverse event profile to placebo (or reference therapy), with the exception of an increased frequency of gastrointestinal symptoms (Table 57.7) [124].

Recent phase 2 RCTs using semaglutide or dulaglutide, two long-acting injectable GLP-1 RAs, have documented possible benefits of these agents on hepatic fat content (assessed by MRI techniques) and histological resolution of NASH in people with NAFLD or NASH [141–143]. Given that liraglutide and other long-acting GLP-1 RAs have been also reported to substantially reduce the risk of major CVD events in people with type 2 diabetes [144, 145], it is reasonable to speculate that these glucose-lowering agents will become a valid treatment option in individuals with NAFLD, especially if they have obesity or type 2 diabetes.

Sodium–glucose cotransporter 2 inhibitors

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are a new class of glucose-lowering agents that increase the glucose reabsorption by the kidneys and also by the bowel and heart [122, 123]. SGLT-2 is particularly expressed on the renal epithelial cells edging the S1 segment of the proximal convoluted tubule and promotes glycosuria [122, 123]. Experimental evidence supports a favourable effect of SGLT-2 inhibitors on liver steatosis, necro-inflammation, and also fibrosis, owing to a combination of negative energy balance by increased glycosuria and substrate switching towards lipids as a source of energy expenditure [146, 147]. In 2020, the results of some systematic reviews and meta-analyses supported the role of SGLT-2 inhibitors (empagliflozin, dapagliflozin, or canagliflozin) in improving serum liver enzyme levels and liver fat content, as assessed by MRI-based techniques (Table 57.7) [124, 148]. However, most of the RCTs available so far are small with a short duration and did not test the efficacy of SGLT-2 inhibitors on liver histology of NAFLD.

Recently, in a single-arm, open-label, pilot trial enrolling Asian individuals with type 2 diabetes and biopsy-confirmed NASH, the authors showed that a 24-week treatment with empagliflozin (25 mg/d) was associated with some improvement in histological scores of NASH [149]. In the published RCTs, SGLT-2 inhibitors had a similar adverse event profile to placebo (or reference therapy), with the exception of increased risk of genitourinary infections (Table 57.7) [124]. Given that SGLT-2 inhibitors also have relevant cardio-renal benefits in large RCTs enrolling individuals with and without type 2 diabetes [150, 151], they are attractive drugs in individuals with NAFLD. Currently, there are ongoing RCTs testing the hepatic effects of different SGLT-2 inhibitors in individuals with biopsy-confirmed NASH.

Lipid-lowering drugs

Statins decrease low-density lipoprotein (LDL) cholesterol by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme-A reductase, which is a key enzyme implicated in cholesterol synthesis [152]. Along with their lipid-lowering effects, statins exert multiple pleiotropic properties, including anti-oxidative and anti-inflammatory effects, reduction of neo-angiogenesis, and improvement of circulatory endothelial function [152]. Although statins may moderately increase serum aminotransferase levels, liver damage due to statins is uncommon [152, 153]. Indeed, it is estimated that an increase of serum liver enzymes >3 times the upper limit of normal is observed in <1% of individuals treated with statins [152, 154]. For this reason, the monitoring of serum transaminase levels is not recommended for individuals treated with statins [152]. *Post hoc* analyses of some published RCTs have documented that statin treatment is safe and can improve liver tests and reduce cardiovascular morbidity in people with mild to moderately abnormal liver tests that are potentially attributable to NAFLD [155]. Preliminary evidence from some non-randomized interventional studies also suggested that in individuals with NAFLD, statin treatment is associated with some improvement in liver steatosis, necro-inflammation, and even fibrosis [156–158], but future *ad hoc* RCTs are needed to confirm the possible hepatic benefits of statins in people with NASH.

Ezetimibe is another lipid-lowering drug that inhibits the small intestinal enterocyte uptake and absorption of cholesterol by binding to Niemann-Pick C1-like 1 (NPC1L1), which keeps cholesterol in the intestinal lumen for excretion. A meta-analysis of six studies (two RCTs and four single-arm trials), involving 273 individuals with NAFLD with and without type 2 diabetes, reported that ezetimibe reduced serum liver enzyme levels and improved hepatic steatosis and hepatocyte ballooning, but not liver fibrosis [159].

Omega-3 (n-3) PUFAs contain several long-chain fatty acids, such as α-linolenic acid, stearidonic acid, eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid [160]. In a recent meta-analysis of 22 RCTs including 1366 participants with and without type 2 diabetes, the investigators reported that n-3 PUFA supplementation reduced liver fat content (on imaging techniques) when compared with placebo [160]. Similar findings were also observed in another meta-analysis [161]. However, it is important to point out that the size of the effect is relatively small, and that the optimal dose, type of n-3 PUFA, and duration of treatment with n-3 PUFAs are not established [161]. One phase 2 RCT testing the effects of high-dose n-3 PUFAs in people with and without type 2 diabetes with NAFLD suggested that docosahexaenoic acid may be more effective than eicosapentaenoic acid in reducing liver fat

content [162]. Hence, well-designed RCTs are still required to address the question of whether a specific type of n-3 PUFA supplementation is beneficial for the treatment of NAFLD in people with or without type 2 diabetes.

Antihypertensive drugs

Some experimental studies in animals showed that angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers exert antifibrotic effects on the liver [163]. However, clinical studies testing the potential antifibrotic effects of these drugs in individuals with NAFLD have produced inconsistent results [164–167]. Future RCTs are required to better clarify this issue.

New drugs for non-alcoholic fatty liver disease

Several other potential drugs have been tested for NAFLD or NASH [137]. However, in most of the published RCTs available so far only a subset of NASH individuals had established type 2 diabetes.

Synthetic ligands activating the FXR improve insulin resistance, regulate glucose and lipid metabolism, and have anti-inflammatory and antifibrotic hepatic effects in animal NASH models [137]. Obeticholic acid (OCA), a synthetically modified analogue of chenodeoxycholic acid, is the prototype for this new class of agents [137]. A phase 2 RCT of 283 individuals with non-cirrhotic NASH (~50% with type 2 diabetes) showed that OCA treatment improved histological features of NASH, including fibrosis [168]. In an 18-month interim analysis of a multicentre phase 3 RCT that included 931 individuals (57% with type 2 diabetes) with biopsy-proven NASH and fibrosis, the investigators reported that OCA (25 mg/d) significantly improved liver fibrosis compared to placebo [169]. However, OCA had some important side effects, including pruritus and elevated plasma LDL cholesterol levels [169]. In this trial, plasma LDL cholesterol levels increased by ~20% from baseline, although it was suggested that the increase tended to be transient and was controlled by statin treatment [169]. The adverse effect of OCA on plasma lipid profile is of clinical importance, as individuals with NAFLD are at high CVD risk.

Conclusion

NAFLD and type 2 diabetes frequently coexist and act synergistically to increase the risk of adverse liver-related and extra-hepatic clinical outcomes. Type 2 diabetes is also one of the strongest clinical risk factors for faster progression of NAFLD to NASH, cirrhosis, and HCC. Strong evidence now indicates that NAFLD is also associated with an increased risk of developing incident type 2 diabetes and contributes to the development of CVD and other chronic vascular complications of diabetes. CVD is the predominant cause of death in people with NAFLD and, therefore, aggressive CVD risk reduction measures and CVD treatments may be required in people with NAFLD, regardless of whether these individuals have coexisting type 2 diabetes.

Since NAFLD is very common in people with type 2 diabetes (affecting up to nearly 70% of these individuals), healthcare professionals need to be aware of how to diagnose NAFLD and the different stages of the liver disease. When NAFLD is diagnosed, lifestyle modifications focused on weight loss and increased physical activity are effective in promoting histological resolution of NASH, particularly in the early stages of the disease. When advanced fibrosis or cirrhosis is present, specialist referral is required, because of the potential risk of portal hypertension, liver failure, and HCC. Randomized controlled trials of existing licensed drugs for the treatment of type 2 diabetes, such as pioglitazone and GLP-1 RAs (e.g. subcutaneous liraglutide and semaglutide), showed that these glucose-lowering agents may be effective in inducing NASH resolution in up to ~50% of individuals with biopsy-proven NASH compared to placebo. It is an exciting time for NAFLD research and, considering the multiple pathways implicated in the pathogenesis of NASH, and the many novel treatments that are being tested in ongoing randomized trials, it is possible that combination therapy might prove to be the most effective strategy for ameliorating NASH in people with type 2 diabetes.

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58 The Skin in Diabetes

Paul Devakar Yesudian
Department of Dermatology, Wrexham Maelor Hospital, Betsi Cadwaladr University Health Board, Wrexham, UK

Key points

- Some of the skin manifestations associated with diabetes may be relatively specific, while others are more common among individuals with diabetes than those without diabetes.
- The skin changes associated with diabetes can be roughly divided into metabolic, vascular, infections, and iatrogenic, though there is considerable overlap between them.
- Acanthosis nigricans, pigmented papillomatous overgrowth of the epidermis seen in flexures, is associated with hyperinsulinaemia.
- Many of the metabolic changes in the skin are related to glycation of structural proteins that occurs more extensively in diabetes.
- Necrobiosis lipoidica is most frequently seen in type 1 diabetes, often on the shins in women. It remains problematic to treat.
- Thickening, loss of elasticity, and yellowing of the skin are related to glycation of collagen and elastin in the skin.
- There are numerous vascular changes in cutaneous vessels with reddening and telangiectasia of the skin similar to premature degenerative ageing of the skin.
- Skin infections, including bacterial, fungal, and yeast, occur more commonly in people with diabetes compared to people without diabetes and tend to be more severe.
- Some skin conditions occur more commonly in people with diabetes compared to the general population, including psoriasis, generalized granuloma annulare, pruritus, perforating disorders, vitiligo, and lichen planus.
- Reactions to recombinant human and analogue insulin preparations and newer classes of anti-diabetes agents are unusual.
- Glues used in newer medical devices in the management of diabetes can cause contact sensitivities.

Many skin conditions are associated with diabetes and occur in about one-third of those affected [1]. Some are relatively specific, usually caused by the metabolic changes in diabetes or side effects of treatment, while others are non-specific but occur more frequently than in individuals without diabetes. Cutaneous changes may be the first sign of diabetes or develop at any time during the course of the disease [2]. As suggested by the aetiopathogenesis, autoimmune skin conditions occur more commonly in people with type 1 diabetes, while infections tend to predominate in type 2 diabetes [3]. The classification used in this chapter, including associated conditions and infections, is shown in Table 58.1.

Metabolic manifestations

This group includes several conditions that appear relatively specific to diabetes (e.g. diabetic thick skin) or are more common than in the general population (e.g. necrobiosis lipoidica) [4]. The aetiology of these conditions is largely related to the process of non-enzymatic glycation of cutaneous structural proteins or hyperinsulinaemia.

Acanthosis nigricans

Acanthosis nigricans is characterized by velvety papillomatous overgrowths of the epidermis, which are usually hyperpigmented. The flexural areas, particularly the axillae, groins, inframammary region, and neck, are most frequently symmetrically affected and may become macerated or malodorous if severe [4] (Figure 58.1). The condition occurs at a higher frequency in skin of colour compared to people of white European ancestry [5]. Rarely, more generalized changes involve the knuckles, other extensor surfaces, palms, and soles. Histological features include extensive hyperkeratosis, papillomatosis, and acanthosis with retained keratotic material (which accounts for the dark colour).

Acanthosis nigricans is associated with various endocrine disorders that share the common features of insulin resistance and hyperinsulinaemia; these include diabetes, acromegaly, Cushing's disease, polycystic ovarian disease, obesity, metabolic syndrome, and genetic and autoimmune insulin receptor defects [6]. The presence of acanthosis nigricans is an independent prognostic indicator for the development of type 2 diabetes [7]. A severe malignant form is associated with gastric adenocarcinoma. Hyperinsulinaemia induced by insulin resistance activates insulin-like growth factor type 1 receptors on various tissues, including epidermal cells and fibroblasts [8]. Stimulation of keratinocyte proliferation gives rise to hyperkeratosis and acanthosis (Figure 58.2).

Acanthosis nigricans, which can be disfiguring and upsetting, is most frequently seen in people with type 2 diabetes and obesity. Management is by dietary alterations, weight reduction in obesity, and increasing physical activity, which can reverse changes to a

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Table 58.1 Cutaneous manifestations of diabetes.

Metabolic manifestations		Acanthosis nigricans	Achrochordons
		Diabetic bullae	Eruptive xanthomas
		Diabetic thick skin	Diabetic scleroderma
		Yellow skin and nails	
Vascular changes		Diabetic dermopathy	Necrobiosis lipoidica
		Facial erythema	Periungual telangiectasia
		Lower-limb vascular changes	Calciphylaxis
Infections	Bacterial	Staphylococcus	Streptococcus
		Erythrasma	Necrotizing fasciitis
		Malignant otitis externa	
	Fungal/yeast	Dermatophytosis	Candida
		Mucormycosis	
Associated conditions		Pruritus	Perforating disorders
		Lichen planus	Vitiligo
		Clear cell syringomas	Glucoganoma
		Disseminated granuloma annulare	Psoriasis
Iatrogenic		Insulin induced	
		Immediate: localized/generalized	
		Delayed: lipodystrophy	
		Reactions to oral anti-diabetes drugs	
		Reactions to medical devices	

(a)

(b)

Figure 58.1 Acanthosis nigricans, showing the typical dark velvety appearance (a) in the axilla; (b) in the groin. Source: (b) Courtesy of Dr S. Mendelsohn, Countess of Chester Hospital, Chester, UK.

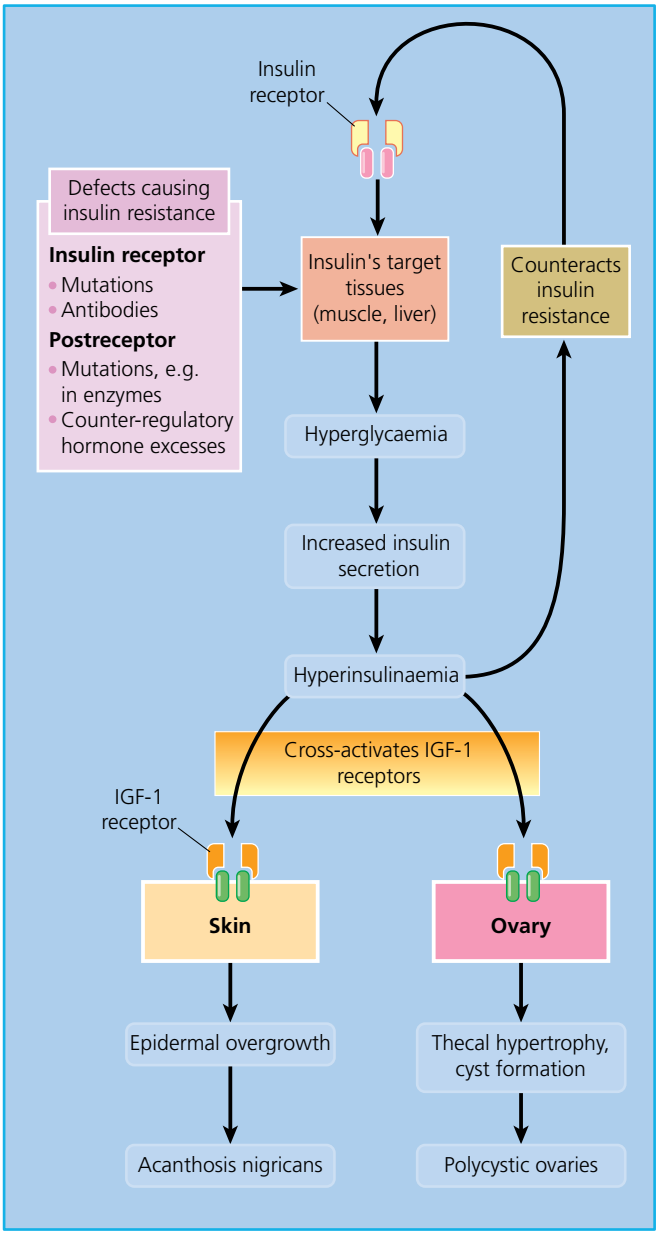

Figure 58.2 Suggested relationship of insulin resistance and hyperinsulinaemia to acanthosis nigricans. Raised insulin levels may act on insulin-like growth factor I (IGF-I) receptors in the skin to cause epidermal overgrowth. Similar events in the ovary could lead to polycystic ovary disease, which is also associated with insulin-resistant states.

certain extent [9]. Topical retinoids, calcipotriol, and mild peeling agents, such as salicylic acid or lactic acid, may be helpful for limited involvement. Systemically, metformin and rosiglitazone reduce insulin levels and give modest improvement in the condition [10].

Achrochordons (skin tags)

Skin tags are benign, soft, fleshy, polypoid skin-coloured fibromas, which occur with increasing age and are particularly common in people with diabetes [11]. They may occur in about 66% of individuals with diabetes and are probably related to the proliferative effect of hyperinsulinaemia on keratinocytes and fibroblasts, as in acanthosis nigricans [12]. Large numbers may be a marker of impaired glucose tolerance [13]. Individuals with more than 30 skin tags and women with lesions under their breasts are particularly prone to diabetes [14]. Skin tags occur predominantly in flexural regions around the eyes, neck, axillae, and in women in the inframammary area. Treatment is usually not required, although snip excision, cryotherapy, or electrodessication is effective if they cause discomfort through irritation or give cosmetic concern.

Diabetic bullae (bullosis diabeticorum)

Diabetic bullae affect men more than women and are more common in older people and those with peripheral neuropathy [15]. The condition usually presents as tense, sterile, asymmetrical blisters, from a few millimetres up to several centimetres in size, on a non-inflammatory base, appearing rapidly and healing over a few weeks without scarring (Figure 58.3). The feet and lower legs are the commonest sites, followed by the hands. The condition is most commonly seen in long-standing type 1 diabetes with late complications. Risk factors include sudden blood glucose changes, magnesium and calcium alterations, microangiopathy, and renal failure [16]. Electron microscopy studies demonstrate a subepithelial split at the level of the lamina lucida and immunofluorescence studies are negative [17]; however, the aetiology of bullae is unclear. Other causes of subepithelial blisters, including the autoimmune blistering diseases porphyria cutanea tarda, pseudoporphyria, and infections such as bullous impetigo, need to be excluded. Treatment is normally supportive to prevent secondary infection, although surgical debridement and negative-pressure dressings have been proposed [18]. Aspirating tense blisters to prevent rupture may be required and most heal within a few weeks.

Diabetic thick skin

The skin of individuals with diabetes is measurably thicker by ultrasound than in people without diabetes [19] and shows loss of elasticity [20]. Thickening is most often seen on the hands and feet and may progress to finger pebbles, groups of indurated papules on the extensor aspect of the fingers and knuckles. Milder changes are

(a)

(b)

Figure 58.3 Diabetic bullae. (a) Acute bullae on an arm. (b) Resolving lesions 14 days later.

seen in a minority of older people without diabetes. Skin thickness is largely attributable to the filamentous proteins of the dermis, of which collagen is by far the most abundant. In people with diabetes, the collagen bundles are thickened and disorganized, as a result of irreversible non-enzymatic glycation and cross-linking of protein. The formation of advanced glycation end-products (AGEs) damages the protein, thereby reducing the ability of enzymes such as collagenase to remodel the fibres [21]. Gradual and irreversible modification of collagen, elastin, and other structural dermal proteins is part of the physiological ageing process, but is accelerated in diabetes, especially if there is persistent hyperglycaemia.

Skin thickness shows some correlation with the duration of diabetes [22] and the presence of complications such as neuropathy and microangiopathy [23, 24]. Topical emollients help with the associated skin dryness, but there is no effective treatment. Rigorous glycaemic management may slow the development of skin thickening. While skin thickness is often clinically insignificant, when advanced it may lead to the specific complications of *diabetic hand syndrome* and diabetic scleroedema [25]. The combination of thick, tight waxy skin and limited joint mobility has been called cheiroarthropathy and is present in up to a fifth of people with type 1 diabetes [26].

Diabetic hand syndrome usually occurs in those over 60 years of age (Chapter 59) [27]. The early changes include thickening of the skin over the dorsa of the hands and digits, especially the proximal interphalangeal joints (sclerodactyly). More extreme cases present with a tight, waxy appearance together with pebbly pads over the knuckles and distal fingers. The interphalangeal joints are particularly susceptible and involvement of periarticular connective tissue contributes to painful stiff fingers [28]. In a minority, the condition progresses to cause a fixed flexion deformity of the fingers and Dupuytren contracture, while soft tissue thickening of the wrist may cause carpal tunnel syndrome by compression of the median nerve.

Scleroedema of diabetes

This is marked dermal thickening, commonly involving the posterior aspect of the neck and upper parts of the back, and extending to the face, arms, and abdomen with more severe involvement, but sparing acral areas. It has a prevalence of 2.5–14% in diabetes and is found particularly in men with type 2 diabetes and those with overweight and persistent hyperglycaemia [29]. The onset is insidious and asymptomatic, but can lead to neck and back pain in severe cases [30]. The skin is hard, thick, and may be indurated and erythematous. Histology reveals dermal thickening that contains large collagen bundles and an increased number of mast cells [25]. The pathogenesis is linked to non-enzymatic glycation of collagen, leading to increased collagen crosslinking and therefore reduced degradation, resulting in increased thickness of the skin [7]. No therapy is particularly effective for scleroedema, although response to ultraviolet light or psoralens with ultraviolet A (PUVA) [31] has been reported. Strict glycaemic management is recommended as this may slow the progression.

Yellow skin

Individuals with diabetes develop yellowish skin and nails more frequently than the general population. This is most noticeable on the palms and soles. It has been referred to as carotenaemia, but there is little evidence to support the theory that carotenoids are the cause [32]. The most probable explanation is that the discoloration is due to non-enzymatic glycation of dermal collagen. The end product 2-(2-furoyl)-4(5)-(2-furanyl)-1H-imidazole has a yellowish colour. This occurs to a much greater extent with the hyperglycaemia of diabetes compared to individuals without diabetes.

Eruptive xanthomas

Eruptive xanthomas are rare and pathognomonic of extreme hypertriglyceridaemia [33]. This can occur at the initial presentation of type 1 diabetes when there is insulinopaenia [11]. Insulin is a stimulatory factor for lipoprotein lipase, which if not activated leads to impaired clearance of very low-density lipoproteins and chylomicrons. Xanthomas present as clusters of yellowish papules of triglyceride up to 5 mm on extensor surfaces of the limbs and buttocks (Figure 58.4). The onset is usually rapid and lesions frequently occur in groups or crops with surrounding erythema. Men are more commonly affected. Although xanthomas may itch initially, they are typically asymptomatic. Rarely, acute presentations can be painful and the Koebner phenomenon, whereby lesions occur at the site of trauma, has also been reported with eruptive xanthomas [34]. Lesions regress slowly within months after hypertriglyceridaemia has been corrected by lipid-lowering drugs, dietary modification, or improved glycaemic levels.

(a)

(b)

Figure 58.4 Eruptive xanthoma: (a) buttocks; (b) knees.

Vascular changes

Diabetic dermopathy (shin spots)

Diabetic dermopathy is the commonest dermatological condition associated with diabetes, occurring in up to 50% of people with diabetes and nearly 3% of the adult general population, who usually have only one or two lesions. By contrast, most individuals with diabetes have four or more [35]. Men are more frequently affected. It is commoner in those over 50 years of age and in long-standing diabetes. The condition is associated with the microangiopathic complications of diabetes such as neuropathy, nephropathy, and retinopathy, and also coronary artery disease [36, 37]. The presence of diabetic dermopathy is a subtle sign that suggests more serious complications [38]. Diabetic dermopathy does not correlate with obesity or hypertension in individuals with diabetes [39]. The presence of microvascular changes, notably thickening of arterioles and capillaries, led to the term *diabetic dermopathy* [40]. It has been hypothesized that diabetic dermopathy arises from local abnormal blood flow. This was confirmed with laser Doppler technology, which revealed a functional abnormality in blood flow in 25 people with diabetes compared to 67 people without diabetes [41].

The lesions are well-circumscribed, atrophic, brownish scars often on the shins, giving the alternative name *diabetic shin spots* [35] (Figure 58.5). The forearms, thighs, and bony prominences may also be affected [39]. The lesions are usually bilateral and may appear in crops. Early lesions are oval, red papules measuring up to 1 cm in diameter, which slowly develop scaling and a brown colour due to the presence of haemosiderin-laden histiocytes and extravasated erythrocytes in the superficial dermis. There is no recommended treatment, as they are usually asymptomatic and tend to resolve over 1–2 years. Variable improvement has been observed with better glycaemic levels [36]. However, it is worthwhile screening for other microangiopathic complications of diabetes [42].

Figure 58.5 Diabetic dermopathy, 'shin spots'. Source: Courtesy of Professor Julian Verbov, Royal Liverpool University Hospital, UK.

Necrobiosis lipoidica diabeticorum

Necrobiosis lipoidica is a chronic granulomatous skin condition that most frequently affects the shins of those with type 1 diabetes. This is a rare condition with a 1% prevalence in people with diabetes [23, 43]. Although it is much commoner in individuals with diabetes, the relationship to diabetes and the aetiology of necrobiosis lipoidica remain unclear. In a retrospective study, only 22% of 65 participants with necrobiosis lipoidica had or developed diabetes in a 15-year follow-up. Necrobiosis lipoidica may precede the onset of diabetes by years, develop concurrently, or arise years later. The presence of necrobiosis lipoidica is thus an indication for investigation of possible diabetes and future monitoring. Necrobiosis lipoidica usually develops in young adults or early middle life, but has also been reported in children with type 1 diabetes [44]. Women are three times more commonly affected than men. There is no proven association with glycaemic levels, but those with diabetes and necrobiosis lipoidica appear to have a higher incidence of chronic diabetes complications such as retinopathy, neuropathy, and microalbuminuria [45]. Though the exact cause of necrobiosis is unknown, it is proposed that microangiopathy, metabolic changes, and trauma could play a role [2].

Necrobiosis lipoidica has a distinctive appearance (Figure 58.6). Early lesions may be rounded, dull red, symptomless papules or plaques that slowly progress to the typical chronic lesion – an oval or irregularly shaped indurated plaque with central atrophy. Necrobiosis lipoidica often has a shiny surface, with prominent telangiectatic vessels crossing over a waxy yellowish central area due to lipid deposition. The margin of lesions may be brownish or red and sometimes with comedo-like plugs, where necrotic material is extruded through the surface. The shin is the most commonly affected site, but the thighs, ankles, and feet may also be affected; lesions rarely occur on the trunk, upper limbs, or scalp [45]. Ulceration occurs in up to 35% of cases and may be very slow to heal. Necrobiosis lipoidica lesions may be partially or completely anaesthetic and alopecia is frequently present. Lesions are variable in number but usually few, and most extend slowly over several years, sometimes coalescing with adjacent areas. Long periods of quiescence may occur or occasionally lesions may heal with scarring. The condition can lead to significant morbidity and can be cosmetically distressing to individuals with diabetes [2]. The diagnosis is usually clinical; a diagnostic skin biopsy is not normally required and may risk ulceration in atrophic lesions. The differential diagnosis of early lesions includes granuloma annulare, cutaneous sarcoid, necrobiotic xanthogranuloma, and diabetic dermopathy.

Histologically, necrobiosis lipoidica lesions comprise foci of degenerate collagen bundles with a hyalinized appearance (necrobiosis), surrounded by fibrosis, with diffuse or perivascular

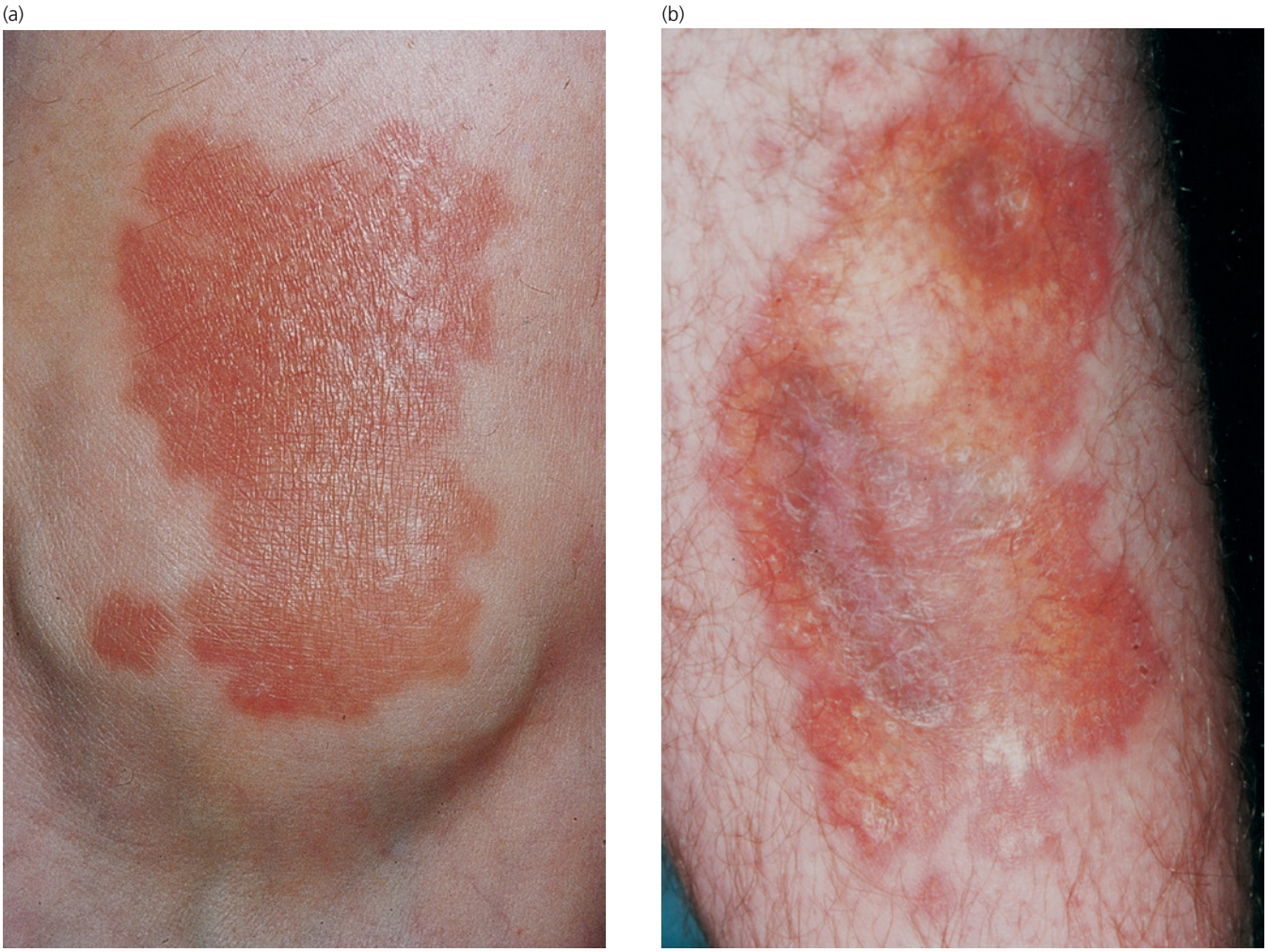

Figure 58.6 Necrobiosis lipoidica diabeticorum. (a) An early lesion on an ankle showing the erythematous stage. (b) A long-standing area of necrobiosis lipoidica; note the typical yellow atrophic appearance with telangiectasia.

infiltrate of histiocytes, lymphocytes, and plasma cells. Frequently a palisading granulomatous reaction with giant cells is seen (Figure 58.7). These abnormalities occur throughout the dermis with telangiectasia and epidermal thinning [46]. There is considerable overlap between these features and those of granuloma annulare. The similarity contributed to the suggestion that localized granuloma annulare is associated with diabetes. Despite histological similarities in the earlier stages of the two conditions, they run different clinical courses and only the generalized form of granuloma annulare is linked to diabetes [46].

No treatment for necrobiosis lipoidica has proved effective in double-blind placebo controlled trials and treatment remains unsatisfactory. Spontaneous remission is unusual and optimal glycaemic management does not usually have a significant effect on the course of the condition. People with diabetes should be encouraged not to smoke and to avoid trauma to the area, which may result in a painful and recalcitrant ulcer. The multitude of case reports of diverse treatments suggests that there is no established benefit for most [4]. In many cases, cosmetic camouflage may be the preferred option. Topical steroids, calcineurin inhibitors, and PUVA are the most-used therapies [47]. For early lesions corticosteroids either applied topically (perhaps under occlusion) or by intralesional injection may be beneficial [48] (Figure 58.8). The

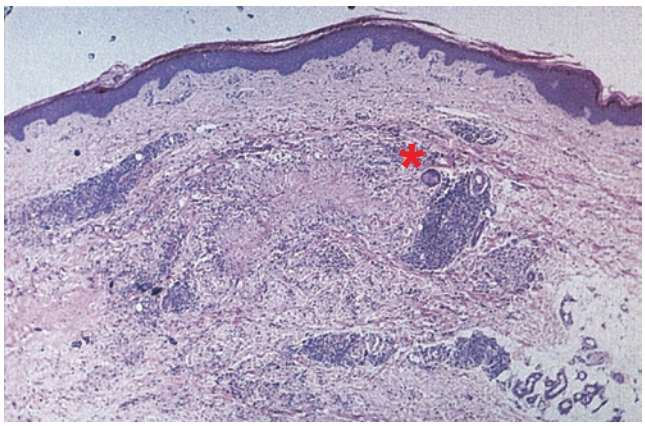

Figure 58.7 Histological feature of necrobiosis lipoidica diabeticorum showing degeneration of the collagen (necrobiosis), associated with fibrosis and a granulomatous histiocytic infiltrate. A giant cell is indicated by the asterisk. Haematoxylin and eosin stain ×40.

inflammatory process extends beyond the clinical margins and topical steroids may halt or slow progression if applied to the periphery of lesions. Once atrophy has developed, it is irreversible and topical steroids should be cautiously used in chronic lesions

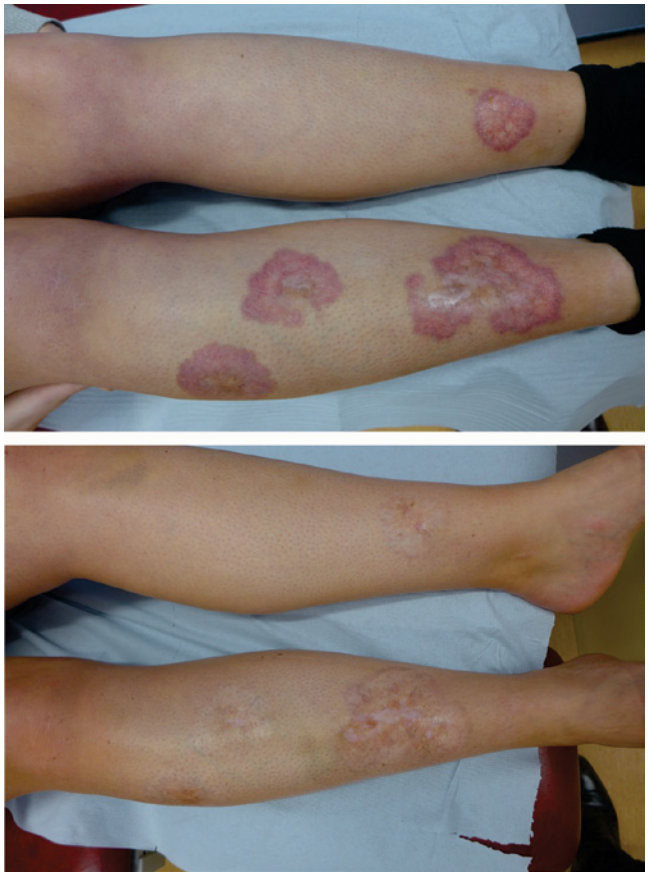

Figure 58.8 Necrobiosis lipoidica diabeticorum treated with intralesional triamcinolone (before and after images). Source: Courtesy of Dr P. Balasubramaniam, Wrexham Maelor Hospital, Wrexham, UK.

because they may worsen skin atrophy. An alternative to topical steroids is the calcineurin inhibitor tacrolimus, which does not cause cutaneous atrophy. Several small open studies report an approximately 50% response rate to topical PUVA [49] while topical retinoids have been beneficial in atrophic cases [50]. Pentoxyphyllin, hydroxychloroquine, and low-dose aspirin are other options [48]. Pulsed dye laser treatment may improve telangiectasia and erythema, but there is a risk of skin breakdown. There are reports of good results following excision and grafting, although the disease may recur locally. The tumour necrosis factor α (TNF-α) antagonists infliximab and etanercept are beneficial for ulcerative necrobiosis lipoidica [51]. Topical application of platelet-rich plasma has shown encouraging results in ulcerated lesions. In an open study, all 15 participants showed marked reduction in ulcer size after 10 weekly applications [52]. Tofacitinib, a Janus kinase inhibitor, has shown promise in treating recalcitrant and ulcerated necrobiosis lipoidica [53, 54].

Rubeosis faciei

Rubeosis faciei (also called rubeosis facie diabeticorum) is the chronic flushed appearance in the face and neck of people with diabetes [55]. The intensity of coloration is dependent on the vascular engorgement in the superficial venous plexus [56]. The changes occur due to altered vascular tone or diabetic microangiopathy. It appears more obvious in fair-skinned individuals and can be difficult to distinguish from normal facial redness in the general population. Rubeosis can be exaggerated by hypertension [57]. The condition may improve with optimal glycaemic management and avoidance of vasodilators (caffeine and alcohol) [42].

Periungual telangiectasia

Erythema of the skin surrounding the nail bed resulting from the dilatation of proximal nailfold capillaries is an excellent marker of functional microangiopathy [58]. It can occur in up to 49% of individuals with diabetes. Even though connective tissue diseases can exhibit similar periungual telangiectases, the lesions are morphologically different. In those with diabetes, isolated homogenous engorgement of venular limbs is seen, whereas mega-capillaries or irregularly enlarged loops are observed in connective tissue disease [59].

Lower-limb vascular changes

An erysipelas-like erythema is described with well-demarcated patches of cutaneous reddening, occurring in the legs and feet of people with diabetes. It can be mistaken for erysipelas, but is differentiated by the lack of associated fever, leucocytosis, or elevated erythrocyte sedimentation rate [60]. Cutaneous signs of ischaemia in the lower limbs include cold or cyanosed feet, erythema, hair loss, and atrophy. A sign of large-vessel disease is dependent rubor with delayed return of colour (>15 s) after pressure has been applied to the skin. Individuals with diabetes who have both venous insufficiency of the lower legs and arterial disease are particularly prone to developing non-healing ulcers; these frequently become superinfected and can be very troublesome to manage. Neuropathy, with lack of pain sensation, also contributes to lower-leg injury and ulceration. Repeated trauma and increased shear forces affect the skin without the usual protective mechanisms that are impaired by peripheral neuropathy, leading to further skin breakdown [59]. The term diabetic foot syndrome encompasses these vascular and neuropathic changes and has a prevalence of between 4% and 10% of those with diabetes [61]. Compared to people without diabetes, the risk for gangrene and amputation is higher in those with diabetes [62]. More detail of the diabetic foot is found in Chapter 53.

Calcific uraemic arteriolopathy (calciphylaxis)

Calcific uremic arteriolopathy is a small-vessel vasculopathy occurring in renal failure and sometimes in those with diabetes. It is characterized by mural calcification, intimal proliferation, fibrosis, and thrombosis [63]. The lesions start as localized areas of erythema and tenderness of the skin that become ischaemic, forming a livedo-reticularis pattern. This leads to the development of subcutaneous nodules and poorly healing, necrotizing skin ulcers that demonstrate black eschars [64]. They can serve as a portal of entry for infectious agents. It typically affects the extremities, but can involve the abdomen and buttocks as well. The prognosis in those with calciphylaxis is poor due to impaired wound healing and infection leading to sepsis. Treatment is usually unsatisfactory. Aggressive analgesic therapy may be required for ischaemic pain, along with optimal blood glucose management and weight reduction [65, 66]. Newer treatments in the setting of renal failure include sodium thiosulphate [67] and cinacalcet hydrochloride [68].

Infections

The relationship between skin infections and diabetes is controversial [69]. Previous studies suggested that there was no significant increase in the prevalence of infections in most people with diabetes

and questioned the strength of assumed associations (Chapter 61) [70]. Hyperglycaemia can increase the risk of infection by causing abnormal microcirculation, decreased phagocytosis, impaired leucocyte adherence, and delayed chemotaxis [71]. Recent literature associates skin infection in diabetes with an immunocompromised state from hyperglycaemia. It is a cause for morbidity and occasionally mortality. Although it can occur in all anatomical sites, the foot is the most commonly affected [72]. Infectious skin diseases, particularly fungal infections, were more common in men compared to women [57]. In a national cohort study in South Korea, the adjusted incidence rate ratio of skin and soft tissue infections was 3.52 times higher in those with diabetes compared to the general population. People with diabetes also had a higher incidence of infection-related hospitalizations [73].

Bacterial infections

Furuncles, carbuncles, folliculitis, and erythrasma were particularly frequent before the introduction of insulin and antibiotics, and skin infections due to *Staphylococcus aureus* are probably commoner in those with diabetes.

Foot infections are the commonest soft tissue infection in diabetes. The area between the web spaces tends to be the portal of entry and staphylococcal infections are the most frequent.

Severe (*malignant*) otitis externa is an uncommon but potentially lethal infection caused by invasive *Pseudomonas* spp. It occurs in older people with diabetes and manifests as purulent discharge with severe pain in the external ear. It progresses from cellulitis to osteomyelitis, meningitis, and cerebritis. Subsequent cranial nerve damage can also occur and carries a high mortality [74]. Treatment involves ear canal irrigation, skin debridement, and systemic antibiotics, particularly quinolones [75].

Erythrasma, caused by *Corynebacterium minutissimum*, is rare and occurs with increased frequency in people with diabetes and obesity. It presents as a red, shiny, or scaly patch in the intertriginous areas and with UV light exhibits a characteristic coral-red fluorescence. Topical or systemic erythromycin is curative. A recent series confirmed the effectiveness of topical mupirocin 2% ointment in this condition [76].

Unusual infections with coliforms or anaerobes occur in those with diabetes, as can *Pseudomonas* infections of the toe web spaces or nailfold (paronychia) and secondary infection of venous ulcers [77]. Anaerobic cellulitis with *Clostridium* spp. can occur in people with diabetic ketoacidosis, requiring aggressive debridement of devitalized tissue, and intravenous antimicrobial therapy [63].

Necrotizing fasciitis is a potentially lethal skin and soft tissue infection that is commoner in people with diabetes [12]. The infection is polymicrobial, including *Streptococcus pyogenes*, anaerobic *Streptococci*, *Bacteroids*, and *Staphylococcus aureus*, and may arise from trivial wounds like injection sites or begin from decubitus ulcers. It presents initially with the triad of pain, swelling, and erythema [78] and can be misdiagnosed as cellulitis (Figure 58.9). An initial clue to necrotizing fasciitis is pain out of proportion to the swelling or erythema with tenderness beyond the apparent involved area (Figure 58.10). Rapid progression ensues, with extensive tissue destruction and severe systemic toxicity, leading to death. Necrotizing fasciitis should be treated with extensive surgical debridement of necrotic tissue and high-dose antibiotics, with blood and tissue culture. The mortality remains high in spite of optimal treatment [79]. This condition should be considered in those with cellulitis who have associated systemic features like tachycardia, leucocytosis, marked hyperglycaemia, or acidosis.

Figure 58.9 Severe infection in a person with diabetes that led to necrotizing fasciitis.

Figure 58.10 Necrotizing fasciitis affecting the chest extending to the skin under the armpit in a patient with suboptimally managed diabetes. Source: Courtesy of Dr A. Nott, Adayar Cancer Institute, Adayar, Chennai, India.

Fungal/yeast infections

Candida

Infection with *Candida albicans* may be a presenting feature of diabetes or manifest as a complication of suboptimally managed diabetes. The infection appears as erythematous papules, coalescing to form glazed plaques, with satellite pustules affecting the flexural areas in the body, the vulva, and penis (Figure 58.11a). In women, vulvovaginitis is the commonest manifestation and presents with pruritus vulvae that can be intense and distressing. The vulva appears erythematous and fissured, with peripheral pustulation in severe cases, and may be particularly troublesome in

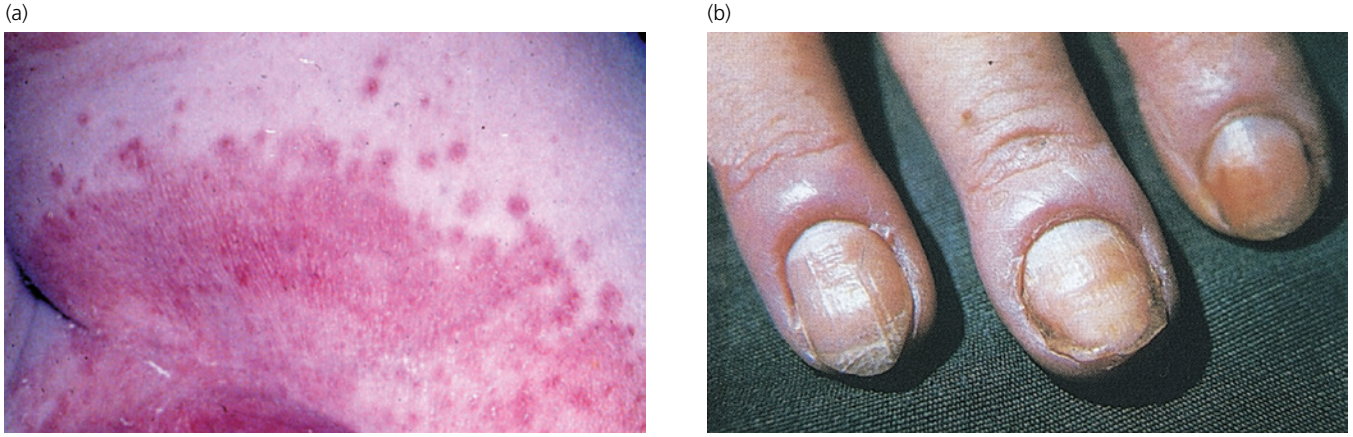

Figure 58.11 Candida infections in people with diabetes. (a) Flexural infection showing satellite lesions. (b) Chronic paronychia caused by *Candida albicans*. Note the swollen and erythematous nailfolds.

hyperglycaemia with glycosuria [12]. Candida balanitis, balanoposthitis, and phimosis occur less commonly in men, but may be a presenting feature [80]. Candida angular stomatitis and an atrophic tongue resembling median rhomboid glossitis are oral manifestations of diabetes. Oral candidiasis occurs more commonly in people with diabetes who smoke or wear dentures [81]. Candida intertrigo occurs on opposing surfaces under the breast, in the groins and axillae, or in the folds of the abdominal skin.

Candida infection of the hands and feet is probably equally seen in people with diabetes as those without, but tends to be more severe in the former. Chronic paronychia presents as swelling and erythema around the lateral nailfold, with more severe involvement leading to onycholysis (Figure 58.11b). Microscopic examination and culture of the extruded material will confirm the infection. Less common than paronychia is infection of the web space between the middle and fourth fingers (erosion interdigitale blastomycetica) [82]. Exclusion of moisture is an essential aspect to the treatment, and systemic antifungal drugs (e.g. oral fluconazole or itraconazole) rather than topical preparations may be required.

Dermatophytosis

Epidemiological studies have shown a higher incidence of onychomycosis in individuals with diabetes; the severity of the nail disease correlates with the duration of diabetes [83]. Fungal skin infection can serve as a portal of entry for other infectious agents, particularly in those with neurovascular complications. *Trichophyton rubrum* is the commonest pathogen, causing erythematous lesions that are often annular with scaly edges. Intertrigo or interdigital infection presents as maceration and superficial scaling. The diagnosis is confirmed by finding fungal hyphae in the superficial scale, ideally taken from the edge of the lesion. Treatment is with a topical imidazole antifungal or terbinafine, although extensive systemic itraconazole or terbinafine may be required. Severe onychomycosis can contribute to foot ulcers and hence require treatment with topical and systemic antifungal therapy, proper nail maintenance, and aggressive debridement [84].

Phycomyces infections

Suboptimal metabolic management, resulting in hyperglycaemia and ketoacidosis, may permit organisms that are normally non-pathogenic to establish infections in traumatized skin [72, 85]. Leg ulcers or non-healing surgical wounds may have super-added phycomycete infections. Deep phycomyces infection like rhinocerebral mucormycosis is a rare but life-threatening complication of diabetes. Early manifestations include facial or ocular pain and nasal stuffiness, which progresses to fever, facial cellulitis, periorbital oedema, proptosis, and rarely blindness [86]. The infection spreads along the turbinates, septum, palate, maxillary and ethmoid sinuses, and can extend into the frontal lobe, cavernous sinus, or carotid artery. It should be suspected in anyone with diabetes presenting with sinusitis, purulent nasal discharge, altered mentation, and infarcted tissue in the nose or palate. Treatment involves correction of acid–base imbalance, aggressive debridement of devitalized tissue, and intravenous antifungal therapy.

Associated conditions

These are a group of dermatoses that are reported more commonly in individuals with diabetes.

Vitiligo

Vitiligo is a common autoimmune condition characterized by complete loss of pigment in the skin. The exact pathogenesis is unknown. It is seen more frequently in type 1 diabetes, but can occur in type 2 diabetes as well. Polyglandular autoimmune syndrome type 2 is characterized by adrenal failure, autoimmune thyroid disease, and type 1 diabetes, and can be associated with vitiligo [87]. It manifests as patchy, symmetrical depigmented areas of skin and, although asymptomatic, can cause significant emotional distress. Treatment is unsatisfactory, although topical steroids and calcineurin inhibitors can be used. People with diabetes should be advised on photoprotection.

Lichen planus

Lichen planus is an inflammatory disorder of the skin recognized by the presence of violaceous flat-topped polygonal papules, distributed in the flexural aspects of the limbs. An increased incidence of diabetes has been reported in people with lichen planus, particularly the erosive oral lichen planus variant [88, 89]. Impaired glucose metabolism is present in half of the individuals and 25% will have overt diabetes [90]. However, most studies have examined the presence of diabetes in those with lichen planus rather than the reverse. The link between diabetes and lichen planus is therefore still unproven, especially since both are relatively common conditions.

Pruritus

Even though there is a common assumption that itching is a symptom of diabetes, this is questionable. Studies have failed to link the presence of generalized pruritus with diabetes [91, 92]. Localized itching, particularly in the genital area, can be associated with candidal infections. The presence of xerotic skin, a feature present in individuals with and without diabetes, can also predispose to pruritus. People with diabetes who are smokers are more likely to experience generalized pruritus compared to smokers without diabetes [93]. It has been hypothesized that sympathetic nerve dysfunction leading to hypohidrosis and dry skin and peripheral sensory neuropathy can contribute to pruritus [94]. Higher postprandial glucose levels are associated with an increased probability of having generalized pruritus in type 2 diabetes [93]. The regular use of emollients ameliorates the itch to a certain extent [95].

Perforating dermatoses

Acquired perforating dermatoses are a group of perforating conditions associated with systemic disease. Reactive perforating collagenosis (folliculitis) is one such condition characterized by transepidermal elimination of degenerative collagen, and is seen in end-stage renal disease caused not only by diabetes but other conditions as well [96]. It presents with pruritic hyperkeratotic papules on the extensor surfaces of the lower limbs, but can occur on the trunk and face. The papules can be pinpoint to about 6 mm in diameter, with central keratotic plugs (Figure 58.12). They sometimes resolve spontaneously, leaving atrophic scars [97]. Histology reveals an atrophic epidermis surrounding a plug of degenerate material comprising elastin and collagen [59]. It is a disorder of keratinization that engenders a proliferation of epidermis to eliminate abnormal tissue. Although it appears to be an inflammatory condition, microvasculopathy has been noted in the underlying dermis of biopsy specimens [98]. The lesions can be exacerbated by injury or excoriation. It is notoriously difficult to treat, but may be helped by topical steroids and retinoids, failing which phototherapy is an option. Intralesional steroid injections and cryotherapy can also be considered. Management of the underlying renal insufficiency or diabetes may be beneficial. The effectiveness of doxycycline and allopurinol has also been documented [99, 100].

Clear-cell syringomas

Syringomas are adnexal non-neoplastic lesions that are derived from the intra-epidermal part of the sweat duct. They present as yellowish papules distributed around the eyes and are asymptomatic. Clear-cell syringoma is an unusual variant that has two features of note: the histological preponderance of clear cells and the frequent coexistence with diabetes [101, 102]. There may be a phosphorylase deficiency secondary to hyperglycaemia that in turn results in the formation of clear cells. Generalized eruptive clear-cell syringomas have also been associated with diabetes [103].

Glucagonoma

The glucoganoma syndrome is caused by tumours of the α cells of the pancreas that secrete glucagon (Chapter 22). Even though the syndrome is rare, it needs to be considered in people with diabetes who present with diffuse atypical rashes. It comprises four major components: increased glucagon levels, diabetes (usually mild), weight loss, and necrolytic migratory erythema. Necrolytic migratory erythema occurs in 70% of cases, manifesting as an annular erythematous and figurate erythema with peripheral vesicles, pustules, and erosions (Figure 58.13). It involves the intertriginous areas and face, but can affect acral sites as well. The dermatosis can be a presenting clue, occurring 1–6 years before the diagnosis of glucoganoma [104]. It can be associated with other physical findings, including glossitis, stomatitis, dystrophic nails, and alopecia. A skin biopsy shows suprabasal acantholysis and psoriasiform hyperplasia with pallor, ballooning, and necrosis of the upper spinous layer of the epidermis [105]. The role of hyperglucagonaemia in the cause of the skin eruption is unclear. Deficiency of essential fatty acids, zinc, and amino acids may be important in the pathogenesis. Resection of the pancreatic islet cell tumour clears the rash, sometimes within 48 hours. Management may also involve chemotherapy, essential amino acid and fatty acid supplementation, and the use of somatostatin or its analogue octreotide, which suppresses glucagon levels and improves skin lesions.

Figure 58.12 Erythematous papules of reactive perforating folliculitis affecting the lower limbs, with some scarring from previous lesions evident. Source: Courtesy of Dr A. Nott, Adayar Cancer Institute, Adayar, Chennai, India.

Disseminated granuloma annulare

Granuloma annulare is an inflammatory condition in the skin characterized by annular erythematous plaques with central normal skin, usually distributed in the extensor aspect of the limbs, particularly in the dorsal hands. The uncommon disseminated form of granuloma annulare has been reported with diabetes [106, 107]. The lesions in the disseminated form are usually asymptomatic and may lack the typical annular morphology. Histology reveals granulomatous infiltration with lymphocytes and histiocytes with central areas of degenerated collagen associated with giant cells. Lesions can resolve

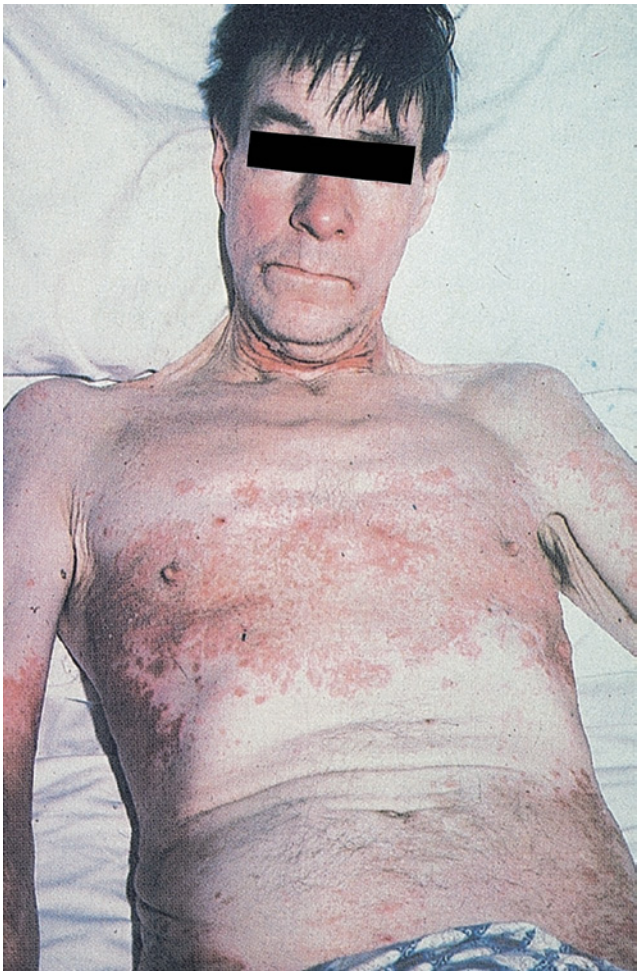

Figure 58.13 Necrolytic migratory erythema in a person with the glucagonoma syndrome. Courtesy of S. Bloom, Royal Postgraduate Medical School, London, UK.

spontaneously or persist for prolonged periods. Treatments include topical steroids, phototherapy, systemic retinoids, antimalarials, dapsone, and topical calcineurin inhibitors [108]. The link between diabetes and generalized granuloma annulare is controversial, with some authors questioning the association [109].

Psoriasis

Psoriasis is a common inflammatory dermatosis affecting about 2% of the world population, characterized by erythematous, scaly plaques predominantly in the extensor surfaces of the limbs. Younger individuals have a higher risk of developing diabetes. There is robust evidence for an association between psoriasis and diabetes [110]. In individuals with psoriasis, diabetes occurs at a twofold increased risk compared to the general population. The strong association with the metabolic syndrome explains the high incidence of diabetes in those with significant cutaneous psoriasis [111]. A recent systematic review and meta-analysis suggests an estimated odds ratio of 1.69 for diabetes in individuals with psoriasis compared to those without [112].

Nail changes in diabetes

The nail manifestations of diabetes can be variable and grouped according to the possible aetiological factors [58]. They are classified as infections, vascular lesions, neuropathic changes, and miscellaneous, although overlap between these factors is common.

Infections

Fungal and bacterial infections occur more commonly in the nails of people with diabetes compared to the general population. Fungal nail infection affects mainly toenails [113]. Studies have shown subclinical onychomycosis in 7.5% of persons with type 2 diabetes [114]. Nails become thick, brittle, and discoloured (whitish or yellowish), with the infection entering beneath the free distal edge of the nail plate. Prompt treatment is recommended and prolonged courses may be required [58]. Drug interactions need to be considered, as azole antifungals like fluconazole and itraconazole can interact with oral anti-diabetes agents.

Bacterial infections with *Staphylococcus aureus*, *Pseudomonas aeruginosa, Proteus vulgaris* and *Escherichia coli* cause an acute paronychia involving the proximal and lateral nailfolds. It manifests as painful swellings of the margins of the nails that can exude pus on pressure.

Candida infection of the nail and surrounding skin may be more prevalent in persons with diabetes [115].

Vascular

Nailfold redness has been observed in diabetes. Nailfold capillaroscopy, a non-invasive method of observing the microvasculature, demonstrates possible characteristic patterns including tortuous, cross-linked capillaries, avascular zones, and ectasias [116]. Thickening of nails with surface irregularities (onychauxis) may be due to vascular insufficiency. Pterygium (scarring of the proximal nailfold to the nail plate) can result from arterial spasm. Reduced circulation to the nail matrix contributes to thin, brittle nails that separate from the nail bed (onycholysis).

Yellow nails have frequently been noted in persons with diabetes, particularly the distal hallux [117]. An early sign of diabetes may be the presence of a yellowish or brownish discoloration in the distal part of the hallux nail plate. The canary yellowish hue that can affect the toe and fingernails is distinct from the yellowish discoloration seen in association with onychomycosis. Yellowish discoloration of the nails could occur from vascular impairment and biochemical changes [118]. While this appearance may give cosmetic concerns, it is benign and there is no effective treatment.

Neuropathy

Diabetic peripheral neuropathy can predispose to thickened nails, abnormal curvature and hypertrophy of the nail plate (onychogryphosis), and increased fragility. Lack of sensation also predisposes to increased infection, ulceration, and changes in the underlying bone.

Miscellaneous

Small, pitted craters on the surface of the nail plate, mostly seen on the middle and ring fingers, are called Rosenau's depressions and can be seen in diabetes [58]. Ingrowing toenails are also seen in type 2 diabetes. The main predictable variables for developing ingrowing nails include increased body mass index, previous trauma, weak dorsalis pedis, onychogryphosis, and subungual hyperkeratosis [119]. Separation of the proximal plate from the nail bed (onychomadesis) may be due to metabolic derangements of diabetes. The appearance of white areas on the nail plate, leuconychia, has been linked to vascular disease seen in diabetes. The glucagonoma syndrome, which predisposes to diabetes, is associated with soft and flexible fingernails [120].

A recent review [121] summarizes the techniques used to detect and monitor diabetes in the nail unit. These include:

- Estimating glycated nail protein (fructosamine) as a reflection of average blood glucose levels. A study of fingernails has shown that people with diabetes have high levels of furosine-lysine, another marker of non-enzymatic glycation [122].
- Analysing the molecular structure of human fingernail proteins (α-helical structure), as people without diabetes do not have α-amide structures.
- Laser-induced breakdown spectroscopy, which can be a screening tool for diabetes in large populations.

Iatrogenic

Reactions to insulin

Insulin allergy

Reactions to insulin were previously common due to the presence of impurities of cow or pig proteins, and preservatives or additives. The use of human and analogue recombinant insulin has decreased the incidence of insulin allergy and it is now less than 1% of people with insulin-treated diabetes [63]. Allergic reactions to insulin can be classified as immediate-local, general, delayed, or biphasic. Immediate-local reactions occur within a few minutes of injection and subside within an hour. Erythema with urtication can occur and is possibly immunoglobulin (Ig)E mediated. Treatment of the immediate local reaction is to change the insulin to a more purified product. Systemic reactions include generalized urticaria and, rarely, anaphylaxis. Generalized urticarial reactions to purified insulins are uncommon [123], but a few people sensitized to animal insulins have suffered anaphylaxis with human insulin [124]. Delayed hypersensitivity reactions are the commonest, appearing about two weeks after the start of insulin therapy. Itchy nodules are evident at the sites of injections, 4–24 hours after injection. Biphasic responses have been reported in some individuals, with immediate urticaria followed by a delayed reaction several hours later. They are considered Arthus-immune complex reactions. The hypersensitivity may be to insulin itself, or to preservatives, such as aminobenzoic acid or zinc [125]. Allergic reactions can be managed by antihistamines, addition of glucocorticoids, discontinuation of therapy, or a change in the insulin delivery system.

Lipoatrophy

Lipoatrophy occurs at sites of insulin injections and is particularly prominent with the longer-acting preparations [126]. It is characterized by a loss of subcutaneous fat and can be a cosmetic concern. This complication is less common with the advent of purer insulins. It is more common in young women with diabetes. The pathogenesis is secondary to an immunological reaction, as biopsies from affected sites show immunoglobulin M and complement. Repeated injections to the same site may predispose to this problem [127].

Lipohypertrophy

Lipohypertrophy presents as soft, subcutaneous nodules or thickening at sites of repeated injections [128]. It occurs due to the lipogenic action of insulin, with repeated local stimulation of adipocytes being causative. As lipohypertrophic areas are relatively painless, young people with diabetes tend to inject the same site repeatedly, worsening the hypertrophy [43]. Insulin absorption may be delayed at such sites, potentially resulting in disruption of glycaemic levels [129]. It resolves spontaneously, usually over a few months, by changing the site of insulin injections. Hyperkeratotic verrucous variants of lipohypertrophy have also been described [130].

Other complications of insulin

Granulomatous lesions that have a furuncular or pustular appearance can occur following insulin injections [131]. Keloids, hyperkeratotic papules, purpura, and localized pigmentation are also reported. Postinflammatory pigmentation following insulin injection is commoner in Asian skin and may take 6–12 months to fade. Epidermal inflammation around an injection site gives hyperpigmentation [43] and contributory factors include intradermal or intraepidermal injections, reuse of needles, non-rotation of injection sites, and occasional injections through clothing. People using insulin pumps for subcutaneous insulin delivery can experience local infections at the site of needle insertion, contact allergy to the associated tape and tubing material, and rarely subcutaneous nodules [132]. Acanthosis nigricans can occur as a local cutaneous side effect to insulin injections; the proliferation of the type 1 insulin-like growth factor (IGF) receptor, epidermal growth factor receptor, and fibroblast growth factor receptor may be causative [43].

Reaction to oral anti-diabetes agents

Sulfonylureas

Sulfonylureas are the most common oral anti-diabetes agents that cause skin reactions. About 1–5% of those taking first-generation sulfonylureas develop cutaneous reactions within two months of treatment [63]. Maculopapular, morbilliform, urticarial, or generalized erythematous reactions are common and resolve with discontinuation of the medication (Figure 58.14). Photosensitive

Figure 58.14 Drug rash with chlorpropamide.

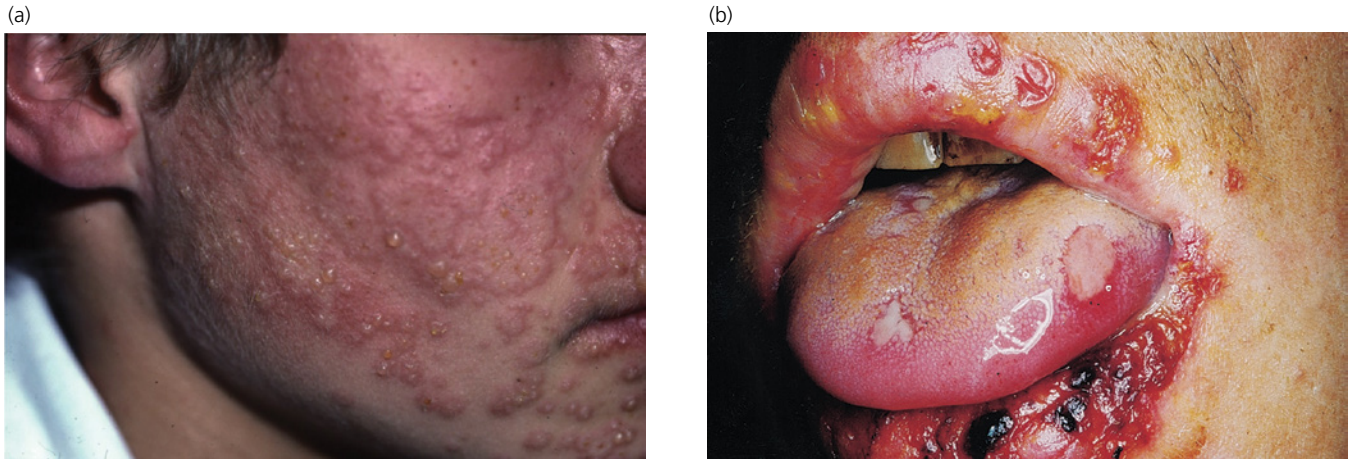

Figure 58.15 Erythema multiforme. (a) The varied appearance of the condition: annular, arcuate, and blistering lesions and confluent erythema on the right side of the face. (b) Mouth ulceration in Stevens–Johnson syndrome, the severe form of erythema multiforme.

reactions, usually of the photoallergic type, as well as lichenoid eruptions have also been reported. Erythema multiforme, characterized by erythematous and haemorrhagic skin lesions associated with *target* lesions, can be a severe manifestation of drug reactions (Figure 58.15). Extensive blistering that includes the mucosal surfaces can occur and if the conjunctiva are involved, urgent ophthalmological opinion is mandatory. The chlorpropamide alcohol flush is a disulfiram-like effect occurring in 10–30% of those taking this drug. Individuals experience facial erythema, headache, and palpitations about 15 minutes after drinking alcohol and it subsides in about an hour. Endogenous opioids may be important, as the flush is blocked by naloxone [133].

Second-generation sulfonylureas like glipizide and glimepiride are less likely to cause cutaneous side effects. Glipizide has rarely been associated with photosensitivity, rash, urticarial, and pruritus. Glimepiride can similarly cause lichenoid skin reactions [134]. Pemphigus and psoriasiform eruptions can be precipitated by glibenclamide [135, 136].

Other oral anti-diabetes agents

Rashes with other oral anti-diabetes agents are much less common than with sulfonylureas. Transient erythema or urticaria may occur with metformin. It is also reported to cause a psoriasiform drug eruption, erythema multiforme [137], photosensitivity, and leucocytoclastic vasculitis [138]. Acarbose can cause a generalized erythema multiforme. As it is minimally absorbed from the gut, it may be the degradation products of acarbose that cause the allergic reaction [139]. Acute generalized exanthematous pustulosis, a dermatosis characterized by generalized pustules all over the body, has been reported to be induced by acarbose [140]. Thiazolidinediones are not commonly associated with reactions, but can cause oedema, transient erythema, and urticaria, as can the glinides such as repaglinide [63].

Dipeptidyl peptidase 4 inhibitors (sitagliptin, saxagliptin, and linagliptin) are associated with an increased risk of developing bullous pemphigoid [141]. Skin-related adverse effects were more common when these drugs were combined. Sodium–glucose cotransporter type 2 (SGLT-2) inhibitors decrease reabsorption of glucose in the proximal tubule, thereby increasing urinary excretion of glucose. This predisposes to urogenital infections, including candida. Other skin adverse effects like generalized rash, urticaria, and eczema have been associated with ipragliflozin [142].

Reactions to medical devices used in persons with diabetes

Various medical devices are currently used in the management of diabetes. Insulin pumps, flash glucose monitoring, and continuous glucose monitoring systems have all been reported to cause skin reactions [143].

Insulin pumps require an adhesive patch on the skin, and this can cause eczematous changes in up to 11% of persons with diabetes [144]. Isoboryl acrylate (IBA) is used in the glue of some devices and can cause an allergic contact sensitivity [145]. Patch testing is a valuable investigation in identifying contact allergy.

Flash glucose monitors are generally fixed on the skin for two weeks. Erythema, itching, and rash can occur with them. Even though it was initially considered an irritant reaction, a recent multicentre study revealed IBA as a potential allergen [146].

Various types of continuous glucose monitoring devices are available and are applied on the skin for between 7 and 10 days. Acrylates used in the glue can cause an allergic contact sensitivity [147].

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59 Bone and Rheumatic Disorders in Diabetes

Andrew Grey[1] and Nicola Dalbeth[2]

[1] Department of Medicine, University of Auckland, Auckland, New Zealand

[2] Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

Key points

- Musculoskeletal disorders may cause pain and disability, and adversely affect management of diabetes.
- Fibroproliferative disorders of soft tissue such as limited joint mobility, frozen shoulder, Dupuytren's contracture, trigger finger, and carpal tunnel syndrome occur more commonly in diabetes and may lead to upper-limb disability.
- Charcot joint is an infrequent but serious complication of diabetic peripheral neuropathy and is characterized by disordered osteoclastogenesis. Bisphosphonate therapy may be a useful adjunct to standard treatment.
- Individuals with diabetes are at high risk of developing gout, particularly in the presence of renal impairment and diuretic use. Treatment with sodium–glucose cotransporter 2 inhibitors may reduce episodes of gout by up to 30%.
- Osteoarthritis is an important cause of poor health-related quality of life in people with diabetes.
- The prevalence of diffuse idiopathic skeletal hyperostosis (DISH) is increased in people with type 2 diabetes.
- Fracture risk is increased in both type 1 diabetes and type 2 diabetes and fracture healing may be impaired in diabetes.
- Bone mineral density is decreased in type 1 diabetes and increased in type 2 diabetes.
- Disease complications increase fracture risk by increasing the risk of falls and causing regional osteopenia.
- Thiazolidinediones decrease bone formation and bone mineral density and increase fracture risk in type 2 diabetes.
- Other anti-diabetes agents do not affect the skeleton.

Musculoskeletal disease in diabetes

A variety of musculoskeletal disorders are associated with diabetes. These disorders may cause pain and disability, and influence the ability of people with diabetes to follow other aspects of diabetes treatment, particularly exercise and weight management. Therapies commonly used in the treatment of rheumatic disease, particularly corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), may be particularly problematic in people with diabetes. The important bone and joint disorders associated with diabetes are discussed in this chapter and are outlined in Table 59.1.

Fibroproliferative disorders of soft tissue

Cheiroarthropathy: limited joint mobility

Limited joint mobility refers to a syndrome of joint contractures resulting in decreased passive mobility of the joints in people with diabetes [1]. Flexion contractures of the proximal interphalangeal joints and metacarpophalangeal joints of the hands are characteristic, with the fifth proximal interphalangeal joint affected first (Figure 59.1). The skin on the dorsum of the hands typically appears tight and waxy [2]. Large joints such as the wrists, elbows, ankle, and cervical spine may also be affected, and reduced lung volumes have been reported in severe cases [3, 4]. Pain is usually mild or absent early in disease, and features of synovitis such as joint swelling, effusion, warmth, and tenderness are typically absent. The disorder can be readily differentiated from systemic sclerosis by lack of Raynaud's phenomenon and other systemic features, normal nailfold capillary examination, and negative autoantibodies [5, 6].

The presence of limited joint mobility of the hands is detected clinically by assessing for the prayer sign or the table-top sign. The prayer sign is positive if the person is unable to oppose the palmar surfaces at any interphalangeal or metacarpophalangeal joints when the hands are placed in the prayer position. For assessment of the table-top sign, the person places both hands on a table top with the palms down and the fingers fanned out. The fingers are then viewed at table level. In stage 0, the entire palmar surface of the fingers makes contact with the table. In stage 1, one finger is affected (usually the fifth proximal interphalangeal joint of one or both hands). In stage 2, two or more fingers of both hands are affected, usually the fourth and fifth proximal interphalangeal joints. In stage 3, there is involvement of all the fingers and restricted movement in a larger joint, usually the wrist or elbow [7]. Passive joint movement should also be assessed to confirm limitation of joint mobility [8].

Prevalence estimates for limited joint mobility in type 1 diabetes range from 9% to 66%, and from 25% to 75% in type 2 diabetes [1, 9–12]. The prevalence rates have declined in individuals with type 1 diabetes in the last 20 years, due to improvements in glycaemic management [13].

Limited joint mobility is an important entity, primarily because of its clinical associations. It is one of the earliest complications of diabetes and is strongly associated with the presence of microvascular complications such as retinopathy and nephropathy in type 1

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Table 59.1 Bone and joint disorders in people with diabetes.

Fibroproliferative disorders of soft tissue
Cheiroarthropathy
Frozen shoulder
Dupuytren's contracture
Stenosing tenosynovitis (trigger finger)
Carpal tunnel syndrome
Disorders of joint tissue
Charcot joint
Gout
Osteoarthritis[a]
Rheumatoid arthritis genetic risk and type 1 diabetes[a]
Disorders of bone
Diffuse idiopathic skeletal hyperostosis (DISH)
Osteoporosis and fractures
Disordered fracture healing

[a] Direct association not proven.

Figure 59.1 Limited joint mobility with flexion contractures affecting the finger proximal interphalangeal joints. Source: Courtesy of Dr Tim Cundy.

diabetes [1, 13–16] and macrovascular complications in type 2 diabetes [10]. It is also associated with other fibroproliferative disorders affecting the upper limb, such as frozen shoulder, Dupuytren's contracture, and carpal tunnel syndrome [12, 16–19]. In general, limited joint mobility does not severely affect hand function, but combinations of these upper-limb disorders may cause upper-limb disability [20–22]. In addition to microvascular complications, risk factors for the development of limited joint mobility in people with diabetes include older age, puberty (in type 1 diabetes), disease duration, and cigarette smoking [10, 23–25].

Advanced imaging techniques have demonstrated thickening of skin, tendons, and tendon sheaths in those with limited joint mobility [26, 27]. Histological examination of the skin shows altered mucopolysaccharide distribution, elastin, and collagen, and reduced vascular lumen [28]. Non-enzymatic glycation and accumulation of collagen have been implicated in the pathogenesis [29]. Disordered glycosaminoglycan metabolism is also a feature; skin biopsies from individuals with severe limited joint mobility show pronounced hyaluronan expression in the epidermis and diminished expression in the dermis and basement membrane, compared with skin from people without diabetes and people with diabetes but without limited joint mobility [30]. In addition, increased urinary glycosaminoglycan excretion has been reported in individuals with limited joint mobility [31]. Reduced circulating insulin-like growth factor I (IGF-I) is associated with limited joint mobility, implicating the growth hormone (GH)–IGF axis in the pathogenesis of this complication [32]. Microvascular abnormalities also contribute to disease, with reports of disordered palmar microvascular flow in response to thermal challenge [33].

The mainstay of therapy remains optimization of glycaemic management, and a reduced prevalence of this disorder has been reported with such interventions [13, 34]. Physiotherapy, particularly hand therapy, may be of benefit to improve joint contractures and function. Corticosteroid injection of flexor tendon sheaths has been reported to lead to resolution of finger contractures in almost two-thirds of cases related to limited joint mobility [35].

Frozen shoulder

This disorder is characterized by shoulder pain, stiffness, and severely restricted range of motion in all planes [36]. Three phases of the disorder are well recognized: first the painful freezing stage with associated nocturnal pain (lasting 4–8 months), followed by the adhesive phase with improvement in pain but severely restricted range of motion (lasting 8–24 months), and finally the resolution phase [37]. The mean time to resolution is 30 months [37]. Plain radiographs of the shoulder are typically normal. Although the condition is usually self-limiting, some people have persistent shoulder pain and restricted range of motion many years after assessment [38, 39].

Imaging and histological studies have demonstrated that the pathological features of frozen shoulder are thickening of the capsule and synovium with contracted joint volume. Affected tissue is characterized by dense type I and type III collagen deposition with proliferating fibroblasts and a chronic inflammatory infiltrate comprising T cells, macrophages, and mast cells [40, 41]. Disordered collagen synthesis and vascular endothelial growth factor 1 (VEGF-1)–mediated angiogenesis have also been implicated [42, 43].

Treatment is tailored to the stage of the disorder [36]. In the painful freezing stage, analgesics, including NSAIDs if tolerated, are indicated. Early use of intra-articular corticosteroids is associated with improved outcomes [44], and physiotherapy with exercise within the limits of pain is of greater benefit than more intensive physiotherapy such as stretching and mobilization [45, 46]. NSAIDs and intra-articular steroids may have similar outcomes over six months [47]. Although oral corticosteroids provide

short-term relief in the painful freezing stage, they are not routinely recommended due to lack of long-term benefit and risk of adverse events [48]. In the adhesive phase, more intensive physiotherapy is indicated. For those who fail to respond to physiotherapy and have persistent shoulder restriction, interventions such as radiographic-guided hydrodilatation, manipulation under anaesthesia, or arthroscopic release should be considered [49, 50].

Diabetes is a major risk factor for frozen shoulder. The prevalence of frozen shoulder is 11–19% of people with diabetes, compared with 2–3% age-matched people without diabetes [17, 20, 51, 52]. Individuals with diabetes are also more likely to have bilateral disease. Key risk factors for frozen shoulder in people with diabetes are older age, duration of diabetes, previous myocardial infarction, retinopathy, and peripheral neuropathy [53]. The presence of other fibroproliferative musculoskeletal disorders such as limited joint mobility and Dupuytren's contracture is strongly associated with frozen shoulder in people with diabetes [53]. Furthermore, frozen shoulder in individuals with diabetes is more difficult to treat due to persistent disease and worse outcomes following surgical interventions [50, 54, 55].

Dupuytren's contracture

Dupuytren's contracture is a fibroproliferative disorder of the palmar fascia leading to the formation of palmar nodules, development of a palmar aponeurosis cord with tethering of the overlying skin, and eventually flexion contractures particularly affecting the ring and little fingers [56]. Older men of Northern European ancestry are most frequently affected. Disordered fibroblast and myofibroblast function has been described, with deposition of type III collagen, potentially mediated by growth factors such as transforming growth factor β (TGF-β) and basic fibroblast growth factor (bFGF) [57–59].

Surgical treatment is the mainstay of therapy, although non-surgical options, particularly local injection of collagenase, are promising [60]. People with diabetes have similar responses to collagenase injections to individuals without diabetes [61]. Splinting and intralesional corticosteroids are frequently ineffective [62]. Surgical referral should be considered in the presence of contracture. Various surgical approaches are available, including fasciotomy (division of the affected palmar fascia) or fasciectomy (excision of the affected palmar fascia). Percutaneous needle fasciotomy is a minimally invasive technique with good short-term outcomes, although recurrence is a frequent problem [63, 64].

Risk factors for Dupuytren's contracture include advanced age, male sex, cigarette smoking, manual labour, and alcohol consumption. Diabetes is also an important risk factor for Dupuytren's contracture, which is present in up to 26% of people with diabetes [20, 21, 65]. Age and disease duration are the major risk factors for development of Dupuytren's contracture in those with diabetes [66]. Dupuytren's contracture is also associated with microvascular complications in type 1 diabetes and macroalbuminuria in type 2 diabetes [67, 68]. Rapidly progressive contractures are less frequently seen in people with diabetes [66]. Coexistent fibroproliferative disease is frequent in individuals with diabetes-associated Dupuytren's contracture, with higher rates of limited joint mobility [68].

Stenosing tenosynovitis (trigger finger)

Trigger finger is a condition in which the flexor tendon is prohibited from gliding through the tendon sheath because of thickening of the synovial sheath over the tendon [69]. This disorder most frequently affects the ring finger, but may also affect the other fingers and the thumb. The person may report a clicking sensation when moving the finger, discomfort over the palm, or overt triggering when the finger is locked in flexion [70]. Nodular or diffuse flexor tendon sheath swelling may be palpable.

The syndrome occurs due to a discrepancy between the flexor tendon and its sheath in the pulley at the level of the metacarpal head [70]. The pulley becomes thickened with increased extracellular matrix and fibrocartilage metaplasia [71]. These pathological changes may be induced by repetitive trauma.

Corticosteroid injection into the tendon sheath is an effective therapy for most individuals, particularly in the presence of nodular disease. For people with nodular disease for less than six months, local injection has a reported success rate of 90% [72]. Splinting and hand therapy are useful adjuncts to local injection. If conservative therapy fails, release using a percutaneous needle approach or open surgery is indicated [73].

People with diabetes are at higher risk of trigger finger, with a lifetime risk of 10% compared with 2.6% of the general population [70]. Multiple finger involvement is also more common in people with diabetes and is associated with the presence of limited joint mobility and carpal tunnel syndrome [74]. A person's age, diabetes duration, and presence of microvascular complications are all associated with increased risk of trigger finger in diabetes [66, 75]. Outcomes are typically worse when trigger finger is associated with diabetes, with lower responses to corticosteroid injection and greater need for surgery [76–78]. Furthermore, type 1 diabetes is associated with a higher prevalence of disease, more affected digits, greater need for surgery, and higher risk of recurrence [66, 76, 78].

Carpal tunnel syndrome

Carpal tunnel syndrome is a common compressive neuropathy affecting the median nerve as it traverses with the flexor tendons through the carpal tunnel, an anatomical space comprising the carpal bones and the transverse carpal ligament [79]. The most common histological appearance is non-inflammatory tenosynovial fibrosis, with increased fibroblast number and type III collagen deposition, most likely mediated by TGF-β [80]. Compression within the carpal tunnel leads to disordered microvascular supply of the nerve, causing demyelination and axonal degeneration. The typical presentation is hand paraesthesia, particularly affecting the thumb, index finger, and middle finger. Paraesthesia is often more frequent at night and may wake the individual from sleep. Wrist and hand pain may also occur, and these individuals frequently report hand clumsiness.

Clinical examination may be normal, but in the presence of severe and prolonged disease there may be features of median nerve denervation, including thenar wasting, weakness of thumb abduction, and sensory loss over the median nerve distribution. Provocative tests including Phalen's test and Tinel's test may be positive, and if present have relatively high specificity for carpal tunnel syndrome. Phalen's test is positive if paraesthesia in the median nerve distribution is reported following flexion of the wrist at 90° for 60 seconds. Tinel's test is positive if paraesthesia is reported after tapping the volar wrist over the carpal tunnel. The diagnosis is confirmed by nerve conduction testing, with the typical findings of prolonged latencies and delayed conduction velocities affecting the median nerve across the wrist [81].

Treatment comprises maintaining the wrist in a neutral position using a removable wrist splint. Splinting is particularly useful for nocturnal symptoms and may be sufficient to treat mild disease [82].

Although oral corticosteroids have short-term efficacy, side effects are usually unacceptable [83]. Local corticosteroid injection provides good short-term relief [84]. Surgical release under local anaesthesia is a well-tolerated and effective therapy, which should be considered when conservative therapy has failed, or in those who have severe symptoms and signs of nerve compression [85]. Open-release and endoscopic approaches have similar clinical outcomes [86].

Carpal tunnel syndrome may be caused by several factors, including non-specific flexor tenosynovitis affecting the wrist, rheumatoid arthritis and other inflammatory synovial arthropathies, obesity, pregnancy, and disordered wrist anatomy [79]. Diabetes is one of the most common metabolic disorders associated with carpal tunnel syndrome, being present in 16% of affected individuals [87]. Most studies have shown increased risk of carpal tunnel syndrome in people with type 1 diabetes or type 2 diabetes [66, 88, 89]. A survey using clinical and neurophysiological assessment reported a prevalence of carpal tunnel syndrome of 2% in a reference population without diabetes, 14% in people with diabetes but no diabetic polyneuropathy, and 30% in people with diabetic polyneuropathy [90]. Carpal tunnel syndrome is associated with duration of diabetes and is more frequently present in those people with microvascular complications such as retinopathy, nephropathy, and polyneuropathy [66, 91]. Carpal tunnel syndrome is also more common in individuals with limited joint mobility, and this disorder may occur at higher frequency in diabetes due to accelerated thickening and fibrosis of the flexor tendon sheaths within the carpal tunnel [19]. Glycation of collagen may also reduce compliance of connective tissue within the carpal tunnel [89]. In addition, the presence of existing microvascular disease may further increase the risk of endoneural ischaemia as the median nerve travels through the carpal tunnel. Carpal tunnel syndrome may be more difficult to assess in people with coexistent diabetic neuropathy, due to atypical presentation and neurophysiological assessment [90, 92]. Treatment options for those with diabetes and carpal tunnel syndrome are similar to those without diabetes, and responses to surgery are usually good [93, 94].

Disorders of joints

Charcot joint

Charcot joint is a destructive arthropathy, most commonly affecting people with diabetes in the presence of severe peripheral neuropathy. This disorder affects 0.1–0.4% of people with diabetes and may lead to severe foot deformity and disability, ulceration, and limb amputation (Chapter 53) [95]. Several stages of disease are described [96, 97]. The developmental stage presents as acute inflammation with swelling, warmth, and erythema of the foot. Pain may be a feature, despite the presence of peripheral sensory neuropathy. Peripheral pulses are usually easily palpable. Gradually worsening deformity occurs, with bone resorption, fracture, and dislocation, leading to instability of the foot and the classic rocker-bottom dislocation of the midfoot (Figure 59.2). Plain radiographs may appear normal early in the acute phase of disease (stage 0), but magnetic resonance imaging (MRI) scans show florid bone marrow oedema, subchondral cysts, and microfractures, and bone scintiscan shows increased uptake in the bony phase [97]. As deformity develops, radiographs show severe osteolysis, bone fragmentation, and disordered architecture (stage 1). In the coalescence phase (stage 2), hyperaemia resolves, swelling reduces, and skin temperature normalizes. Bone debris is resorbed and bone sclerosis may occur. The reconstructive phase (stage 3) is characterized by remodelling of bone, ankylosis and proliferation of bone, and formation of a stable foot. The acute phase (stages 0 and 1) typically lasts 2–6 months, and the reparative phase (Stages 2 and 3) lasts up to 24 months. During both the acute and the reparative phases of disease, bony deformity may lead to abnormal load bearing, with ulceration of overlying skin and secondary osteomyelitis.

Five separate patterns of foot involvement are identified in people with diabetes [98]:

1. Affecting the forefoot with osteolysis of the metatarsophalangeal and interphalangeal joints of the feet, leading to a *sucked candy* appearance on plain radiography.
2. Affecting the tarsometatarsal (Lisfranc's) joint, leading to instability, subluxation, and fracture (Figure 59.2).
3. Dislocation and fracture affecting the midtarsal and naviculocuneiform joints.
4. Affecting the ankle and subtalar joints, often with severe osteolysis.
5. Affecting the calcaneus.

The most common patterns are (2) and (3), and combinations of patterns may be present. Bilateral disease is present in one-quarter of individuals. Rarely, other joints such as the knees, elbows, and shoulders are affected.

The aetiology of the disease remains controversial [99]. Minor trauma frequently precipitates onset of disease and may lead to subclinical bone injury that triggers an aberrant inflammatory response [100]. It is likely that disordered weight bearing in joints affected by peripheral neuropathy leads to repetitive injury and instability (the neurotraumatic hypothesis). Additionally, autonomic dysfunction causing vasodilatation, arteriovenous shunting, and hyperaemic bone resorption has been implicated (the neurovascular hypothesis). Development of osteopaenia and osteolysis increases the risk of fractures in the presence of abnormal load bearing with a cycle of joint instability and fracture development, causing further abnormal load bearing [101]. Advanced imaging and histological analysis have demonstrated local inflammation of synovium and bone in Charcot joints, which is characterized by increased expression of the pro-inflammatory cytokines, tumour necrosis factor α (TNF-α) and interleukin-1 (IL-1) [102–105]. Large numbers of osteoclasts are present within affected bone, and

Figure 59.2 Plain radiograph of Charcot foot. Note the osteolysis, bone fragments, subluxation, and fracture affecting the tarsometatarsal joints of the foot. Source: Courtesy of Dr Tim Cundy.

people with Charcot joint have greater circulating pre-osteoclast cells with increased ability to form peripheral blood-derived osteoclasts *in vitro*, compared with people with diabetes but without Charcot arthropathy and those without diabetes [105–107]. Markers of bone resorption are increased in people with acute Charcot joint [108]. Interestingly, acute-phase markers are not significantly elevated, indicating an apparent dissociation between local and systemic inflammatory disease [109]. These data implicate receptor activator of nuclear factor-κB (RANKL)-mediated osteoclastogenesis, driven locally by pro-inflammatory cytokines, and provide a rationale for the use of agents that target the osteoclast in treatment of the disease.

Management of Charcot joint depends on the stage of disease. Treatment during the acute phase involves immobilization, which reduces inflammation, prevents abnormal load bearing, and stabilizes the foot in a position of least deformity. The standard immobilization method during the acute phase is a non-weight-bearing total-contact cast. This treatment requires close monitoring and regular adjustment, and should be maintained until swelling and temperature normalize and radiographs show no further bony destruction [110]. The use of a weight-bearing total-contact cast may be an acceptable alternative to the non-weight-bearing option, but controlled trials are not yet available [111, 112].

The recognition that the acute phase of Charcot joint is associated with excessive osteoclast activity has led to the testing of agents targeting bone turnover for this condition. Clinical trials of bisphosphonate treatment have shown varying results, with improvement in skin temperature and bone turnover markers, but no clear benefit in immobilization rates [113]. One randomized placebo-controlled trial reported increased immobilization times following zoledronate (3 × 4 mg infusions) [114]. A randomized trial of intranasal calcitonin demonstrated efficacy with respect to bone turnover markers, but no differences in clinical measures were reported [115]. The efficacy of TNF inhibitors and other anti-resorptive agents such as the RANKL inhibitor denosumab has not yet been studied in Charcot joint.

Surgery is generally not considered first-line therapy, although one study has reported good surgical outcomes following debridement, open reduction, and internal fixation with autologous bone grafting in the acute phase of disease [116]. In general, surgical management is currently recommended for those in the reparative (rather than the acute) phase of disease, and particularly for deformities associated with chronic foot ulcers and joint instability. Many different surgical approaches to arthrodesis have been described, including open reduction with both internal and external fixation, depending on the presence of local infection and other anatomical variables [117]. Other surgery includes exostotomy, osteotomy, intramedullary rodding, and amputation. Infection, non-union, and triggering of an acute Charcot reaction are important postoperative complications, and careful postoperative management is essential.

Outcomes in people with Charcot foot are frequently poor. An analysis of 115 individuals reported that non-operative management was associated with a 2.7% annual rate of amputation, a 23% risk of requiring bracing for >18 months, and a 49% risk of recurrent ulceration [118]. The presence of open ulcers at initial presentation or chronically recurrent ulcers is associated with an increased risk for amputation.

Gout

Gout is an inflammatory arthritis caused by intra-articular deposition of monosodium urate crystals [119]. This disorder is the commonest form of inflammatory arthritis in men and affects 1–2% of the white European adult population [120]. In early disease, gout presents as recurrent episodes of self-limiting acute inflammatory attacks (*flares*) of arthritis. These attacks most often affect the first metatarsophalangeal joint, midfoot, and ankle. In the presence of prolonged hyperuricaemia, some individuals develop recurrent polyarticular attacks, tophaceous disease, and erosive arthritis (Figure 59.3).

The key risk factors for gout are hyperuricaemia, male sex, chronic renal impairment, hypertension, obesity, diuretic use, coronary heart disease, and seafood, meat, and alcohol intake [121–123]. The relationship between gout and metabolic syndrome is well recognized. Serum urate concentrations and gout are strongly associated with abdominal adiposity and predict the development of type 2 diabetes [124–126]. The metabolic syndrome and type 2 diabetes

Figure 59.3 Tophaceous gout of the hands in a person with type 2 diabetes.

are more common in people with gout [127]. Promotion of renal tubular reabsorption of uric acid by insulin may mediate this relationship [128]. Recent identification of the glucose and fructose transporter SLC2A9 as a key regulator of serum urate concentrations suggests a further aetiological link between hyperuricaemia and hyperglycaemia [129]. The prevalence of gout is up to 22% in people with type 2 diabetes treated in secondary care [130]. Key risk factors for gout in this population were male sex, renal impairment, and diuretic use. Interestingly, severe hyperglycaemia may reduce urate concentrations, as glycosuria has a uricosuric effect. Thus, as glycaemic levels improve in individuals initiating treatment for diabetes, there is a potential risk of increasing serum urate concentrations and worsening gout attacks [131, 132].

Long-term urate-lowering therapy is indicated for individuals with gout who have recurrent flares, tophi, chronic kidney disease, or urolithiasis [133]. Serum urate lowering to below 0.36 mmol/l (6 mg/dl) is needed to dissolve monosodium urate crystals, prevent flares, and achieve tophus regression. Allopurinol is the mainstay of urate-lowering therapy, but may be ineffective at recommended doses. If the serum urate target is not achieved with allopurinol alone, further options include dose escalation of allopurinol, addition of a uricosuric agent such as probenecid or benzbromarone, or consideration of the xanthine oxidase inhibitor febuxostat, which provides effective urate lowering in people with diabetes and gout [134]. Treatment options for acute gout flares include NSAIDs, corticosteroids, and/or colchicine [135]. Initiation of urate-lowering therapy is frequently associated with exacerbation of gout flares; this side effect can be avoided by commencement of urate-lowering therapy once the acute flare has resolved, gradual introduction of the urate-lowering drug, and co-prescription of low-dose colchicine.

The presence of coexistent gout has several implications for individuals with type 2 diabetes. Poorly controlled gout may hinder attempts at exercise and weight loss. For those with morbid obesity and diabetes, bariatric surgery may have beneficial effects not only on glycaemia and blood pressure, but also on control of serum urate [136]. Diuretic therapy may exacerbate hyperuricaemia and should be avoided in individuals with gout unless absolutely required. Drugs such as losartan and fenofibrate have weak urate-lowering effects and may be of particular benefit in people with diabetes and gout if antihypertensive or lipid-lowering therapy is required [137, 138]. Treatment of type 2 diabetes with sodium–glucose co-transporter 2 (SGLT-2) inhibitors, in contrast to glucagon-like peptide 1 (GLP-1) receptor agonists, may reduce episodes of gout by up to 30% [139, 140].

Osteoarthritis

Osteoarthritis is the most common form of arthritis and is a major cause of pain and disability worldwide. In people with diabetes, the presence of osteoarthritis leads to substantially lower health-related quality of life [141]. Increased load bearing of articular cartilage is a key risk factor for the development of osteoarthritis, and a strong positive relationship has been reported between obesity and the risk of developing osteoarthritis [142–145]. There has been substantial uncertainty about whether type 2 diabetes is an independent risk factor for the development of osteoarthritis [142, 144, 146, 147], or whether the association between type 2 diabetes and osteoarthritis is primarily mediated through increased body mass index (BMI). However, MRI studies of knee cartilage have shown that diabetes is associated with higher T2 relaxation times (indicating increased cartilage degeneration), even after adjusting for other metabolic features including abdominal circumference [148]. Diabetes is also an independent risk factor for severe osteoarthritis requiring arthroplasty, even after adjusting for BMI [149]. Furthermore, the presence of metabolic syndrome and diabetes increases the risk of knee osteoarthritis in women with obesity, even after adjusting for age and joint asymmetry [150]. Chondrocytes express glucose transporters and hyperglycaemia has several direct and indirect deleterious effects on articular cartilage [151]. Inadequately controlled osteoarthritis pain is more frequently observed in people with diabetes at both the knee and the hand [152, 153].

A holistic approach to osteoarthritis management is recommended, with education, exercise, and weight loss if overweight within the core management recommendations for all people with osteoarthritis [154]. Analgesic approaches include topical NSAIDs, which are generally well tolerated in people with diabetes [155]. Intra-articular steroids may provide short-term analgesia in symptomatic knee osteoarthritis, but can lead to short-lived elevations in blood glucose among people with diabetes [156]. For those undergoing hip and knee arthroplasty, diabetes is associated with higher risk of prosthetic infection, postoperative activity limitation, and need for early revision [157–159].

Rheumatoid arthritis

Rheumatoid arthritis and type 1 diabetes share several genetic associations such as *PTPN22*, *HLA-DR9*, the chromosome 4q27 region, the *IDDM5* region, and the *IDDM8* region [160–164]. There is evidence of familial clustering of these disorders: 2.8% of first-degree relatives of probands with rheumatoid arthritis have type 1 diabetes, compared with 0.35% of the general population [165]. The presence of type 1 diabetes is a risk factor for a particular subset of rheumatoid arthritis: anti-cyclic citrullinated peptide (CCP)–positive disease [166]. Anti-CCP antibodies are associated with an increased risk of persistent arthritis in individuals presenting with early inflammatory arthritis [167] and the development of erosive disease in those with established rheumatoid arthritis [168]. The association between type 1 diabetes and anti-CCP–positive rheumatoid arthritis is in part related to the effects of *PTNP22* variants on the risk of both conditions [166].

Skeletal disease in diabetes

Diffuse idiopathic skeletal hyperostosis

Diffuse idiopathic skeletal hyperostosis (DISH) is a disorder characterized by increased bone formation, particularly at the entheses (the insertions of ligaments and tendons into bone) [169]. Ossification of the anterior longitudinal ligament of the spine occurs, most commonly in the thoracic spine (Figure 59.4). Extraspinal ossification may also be identified. The prevalence is as high as 15% in women and 25% in men over the age of 50 years [170]. These individuals may present with back pain and stiffness, although it remains controversial whether DISH is associated with increased back pain, and the disorder is frequently detected as an incidental finding on chest radiographs [171, 172]. Rare complications such as dysphagia, vocal cord paralysis, compression of the inferior vena cava, and neurological compression syndromes have been described in those with florid hyperostosis [173]. Spinal fracture may occur after relatively minor injury and cause significant neurological compromise [174]. The diagnosis is made radiographically, according to the Resnick criteria [175]:

- Presence of flowing calcification and ossification along the anterolateral aspects of at least four contiguous vertebral bodies.

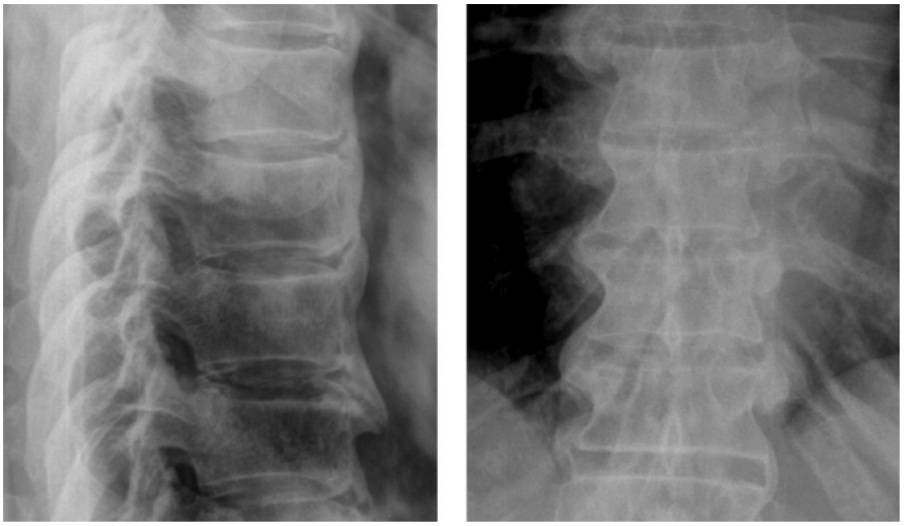

Figure 59.4 Plain radiographs of diffuse idiopathic skeletal hyperostosis (DISH) affecting the thoracic spine. Source: Courtesy of Dr Anthony Doyle.

- Relative preservation of intervertebral disc height and the absence of extensive degenerative disc disease.
- Absence of features of spondyloarthropathy.

There have been no controlled trials of therapies for DISH. For symptomatic individuals, analgesics and physiotherapy are standard therapy. A small uncontrolled study reported that a physiotherapy programme focusing on spinal mobility, stretching, and strengthening had some benefits in improving lumbar spinal mobility after 24 weeks, with no significant benefits in pain or functional outcomes [176]. Surgery is rarely required, but may be indicated for compressive syndromes caused by florid hyperostosis.

Obesity and type 2 diabetes are key risk factors for DISH [177–180]. The presence of additional metabolic disorders such as dyslipidaemia or hyperuricaemia further increases the risk of DISH associated with diabetes [181]. People with DISH have higher rates of hyperglycaemia and higher circulating insulin levels, particularly after a glucose load [178, 182]. Obesity has direct biomechanical effects, due to increased load at the entheses. Additionally, systemic factors may contribute to the development of DISH, as people with this disorder have increased bone mineral density (BMD) elsewhere in the skeleton [183, 184]. Insulin, growth hormone, and IGF-I have been implicated in the pathogenesis of DISH, and high circulating concentrations of these hormones may contribute to the development of hyperostosis [182, 185, 186]. High expression of NF-κB, platelet-derived growth factor BB (PDGF BB), and TGF-β1 has also been reported in affected tissue in people with DISH, implicating these factors in osteoblast activation and new bone formation [187].

Osteoporosis and fractures

Fragility fractures are a major cause of morbidity and public health expenditure. The most devastating fracture, that of the proximal femur, is associated with a 20% risk of dying within six months of the event, and a substantial risk of loss of independence [188]. Individual fractures are associated with considerable periods of disability and loss of productivity [189]. Important risk factors for fragility fracture include older age, low BMD, female sex, light body weight, previous fracture during adulthood, cigarette smoking, falls, and glucocorticoid use [188]. Dual-energy X-ray absorptiometry (DEXA) is the preferred modality for measurement of BMD. Recently, absolute fracture risk algorithms have been developed, using these risk factors, to provide 5–10-year estimates of the risk of major osteoporotic fracture, or specifically of hip fracture [190, 191].

Insight into the mechanisms by which bone loss occurs can be gained by measurement of biochemical markers of bone turnover, which reflect either osteoblast function/bone formation or osteoclast function/bone resorption. At present, bone markers are important tools in evaluating the pathogenesis and treatment of osteoporosis in clinical studies, but their utility in the management of individual patients is limited by assay variability, low predictive value for skeletal events, and high cost [192].

The risk of fragility fractures is increased in both types of diabetes, albeit perhaps by different mechanisms. In addition, attention has focused recently on the skeletal effects of treatments for type 2 diabetes, in particular thiazolidinediones.

Fracture epidemiology in diabetes

Type 1 diabetes

Meta-analyses of observational studies have examined the relationship between type 1 diabetes and risk of fracture [193, 194]. Hip fracture is the only fracture type evaluable in these analyses, because of the paucity of studies of other fracture types. Both meta-analyses demonstrated a substantially increased (6–9-fold) relative risk of hip fracture in type 1 diabetes [193, 194] (Figure 59.5). Studies of other fracture types in type 1 diabetes generally support the notion that non-vertebral fracture risk is increased, with relative risk estimates of 1.3–3 for any fracture [195, 196] and of 2.4 for foot fractures [197]. The only study to date to assess vertebral fractures found no increase in risk in type 1 diabetes [198].

Type 2 diabetes

Epidemiological studies have also suggested that fracture risk is increased in type 2 diabetes. Meta-analyses of observational studies report increased risk of all fractures, and also those of the hip, forearm, and foot [193, 194] (Figure 59.5). Relative risk estimates for hip fracture are lower in type 2 diabetes (1.4–1.7) than in type 1 diabetes, and estimates of fracture risk at other sites in type 2 diabetes range from 1.2 to 1.4. Since the meta-analyses were published, the Women's Health Initiative (WHI) Observational Study, which included >5000 postmenopausal women with type 2 diabetes,

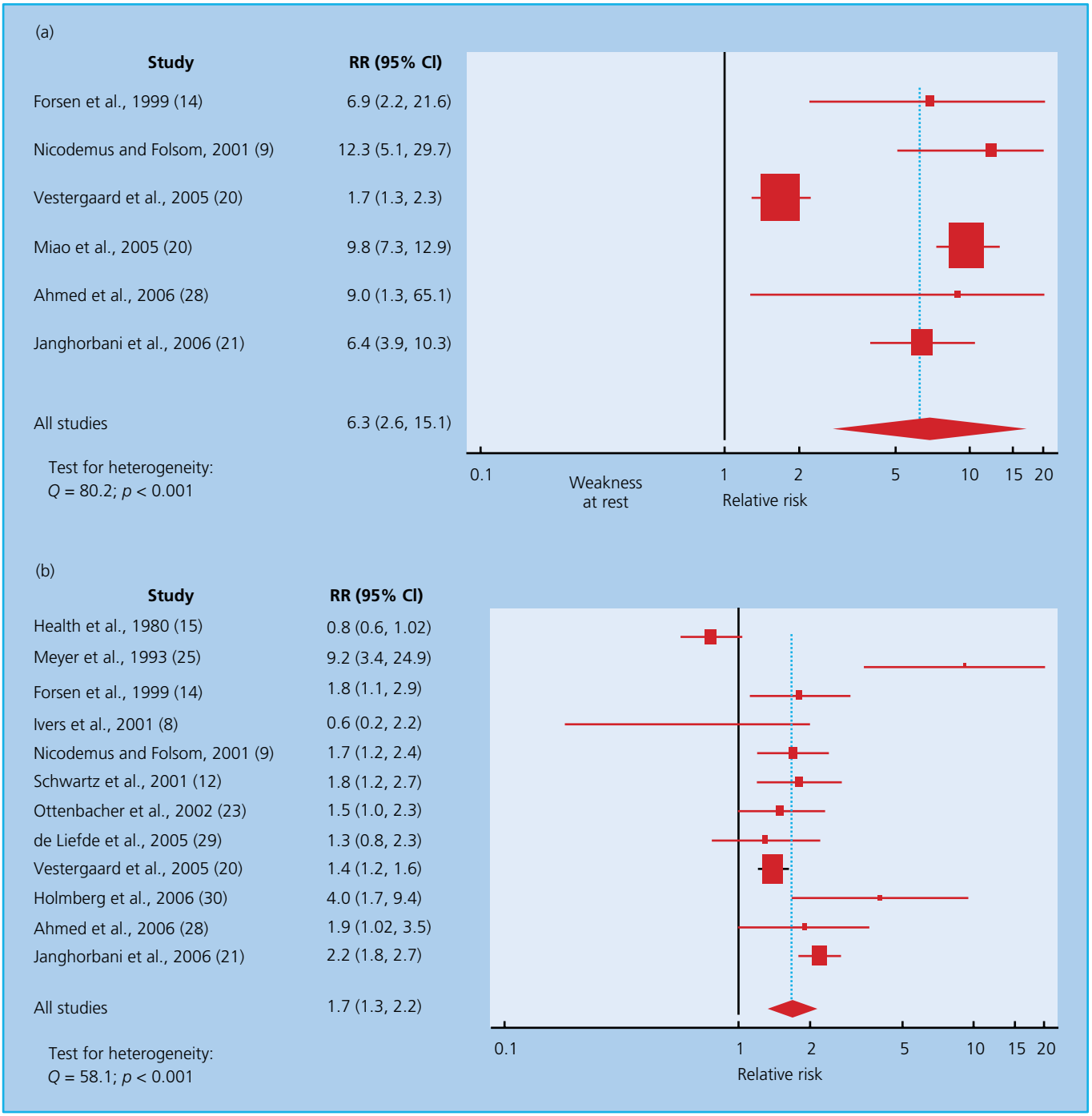

Figure 59.5 Association of (a) type 1 diabetes and (b) type 2 diabetes with hip fracture risk in meta-analyses of case–control and cohort studies. Each square shows the study-specific relative risk (RR) estimate (the size of the square reflects the study-specific statistical weight; that is, the inverse of the variance) and the horizontal line shows the related 95% confidence interval (CI). The diamond shows the summary RR estimate and its width represents the corresponding 95% CI. For details of the studies referred to, see [194]. Source: Janghorbani et al. 2007 [194]. Reproduced by permission of Oxford University Press.

reported increased risks of any fracture and of fractures at several specific sites, including the hip, spine, foot, and upper arm [199]. Risk estimates ranged from 1.2 to 1.5 across the skeletal sites. The WHI study was one of the few with the capacity to evaluate vertebral fractures. Although there was an increased risk of spine fractures in the WHI study, it remains uncertain whether risk of this fracture type is higher in type 2 diabetes, as other studies have not found an association [200].

Mechanisms of skeletal fragility in diabetes

Although fracture risk appears to be increased in both type 1 diabetes and type 2 diabetes, important differences may exist in the pathogenesis of skeletal fragility in the two conditions (Table 59.2). At least two mechanisms underlie the increased skeletal fragility in type 1 diabetes. Most cross-sectional studies of people with type 1 diabetes report decreased BMD throughout the skeleton, although there is no consistent association between age of participants, dura-

Table 59.2 Mechanisms of increased skeletal fragility in diabetes.

Type 1 diabetes	Type 2 diabetes
Decreased BMD	Regional osteopenia
Lower body weight	Secondary to neuropathy
Pancreatic β-cell hormone deficiency	
Low insulin-like growth factor I	
Regional osteopenia secondary to neuropathy	
Increased falls risk	Increased falls risk
Disease complications	Disease complications
Hypoglycaemia	Hypoglycaemia
Other medications	Other medications
Decreased bone quality	Decreased bone quality
Advanced glycation end-products	Advanced glycation end-products
	Disease treatment
	Thiazolidinediones

tion of disease, and magnitude of BMD deficit [201, 202]. Interestingly, studies performed in children and young adults demonstrate lower than normal BMD at hip and spine at the time of diagnosis [203, 204]. Taken together with the observations from longitudinal studies that BMD does not progressively decline in type 1 diabetes [205–208], and cross-sectional studies of middle-aged people with type 1 diabetes that report normal levels of bone turnover markers [209–211], the observed deficit in BMD in type 1 diabetes occurs early in the course of the disease, and perhaps prior to clinical presentation. It is possible that deficiency of insulin and other pancreatic β-cell hormones such as amylin and preptin, each of which has been implicated in skeletal homeostasis [212–215], contributes to the decreased BMD in type 1 diabetes. Low IGF-I levels have been implicated in the pathogenesis of cortical bone loss in type 1 diabetes [216]. Insulin deficiency alone is probably not sufficient to explain the lower BMD, since insulin therapy does not normalize BMD. Lower body weight may also be a factor, as there is a strong positive relationship between weight and BMD [217, 218].

The magnitude of the reduction in BMD (3–8%) is probably insufficient to explain the higher rates of fracture in type 1 diabetes [202]. A second mechanism by which skeletal fragility is likely to be increased is via an increased propensity to falls as a result of disease complications. Neuropathy, visual impairment, cerebrovascular disease, and hypoglycaemia are likely to increase falls risk. In the one study that has evaluated this possibility, substantially higher risks of hip fracture were seen in individuals with type 1 diabetes with a range of diabetes-related complications than in those without complications [219]. Neuropathy may also have an adverse impact on BMD in the distal limbs, as people with type 1 diabetes and neuropathy have lower cortical bone mass in the distal limbs than those without neuropathy [220]. Animal studies suggest that interruption of nerve supply to bone decreases regional bone mass independent of changes in mechanical loading [221]. The presence of regional osteopenia may contribute to the increased risk of distal limb and foot fractures in type 1 diabetes.

The mechanisms by which skeletal fragility is increased in type 2 diabetes are uncertain (Table 59.2). The observation that fracture risk in increased is surprising, because the higher body weight that commonly accompanies type 2 diabetes might be expected to preserve bone mass and protect against adverse skeletal outcomes. In fact, BMD in the axial skeleton *is* higher in people with type 2 diabetes than in those without diabetes [193, 199, 200]. However, BMD remains an important risk factor for fracture in type 2 diabetes, since incident fractures occur more frequently in people with type 2 diabetes and decreased BMD than in those with normal BMD [222]. The limited available evidence suggests that people with type 2 diabetes who have neuropathy and nephropathy have lower BMD than those free of these complications [193, 223].

As in type 1 diabetes, it is likely that complications of type 2 diabetes, such as neuropathy, vascular disease, and impaired vision, increase the risk of falling, and thereby of fracture. In the Study of Osteoporotic Fractures, a prospective study of fracture epidemiology in older American women, participants with type 2 diabetes had a 22% higher risk of non-spine fractures than participants without diabetes [200]. Participants with type 2 diabetes who were treated with insulin had both a higher prevalence of disease complications and a higher risk of fracture than those with type 2 diabetes who were not treated with insulin. In the Health, Aging and Body Composition (Health ABC) study, a prospective study of older (>70 yr) American men and women, there were strikingly higher prevalences of neuropathy, cerebrovascular disease, and falls in participants with type 2 diabetes who suffered a fracture, compared to those with type 2 diabetes who did not fracture [222]. Many risk factors for falls, including use of medications associated with increased falls risk, are more commonly present in populations with type 2 diabetes than in those without diabetes [224]. Low-impact falls are more frequent in individuals treated with insulin [225]. Curiously, however, adjusting for diabetes complications and/or falls risk does not necessarily attenuate the increased fracture risks seen in type 2 diabetes [200, 222].

It is possible that aspects of bone strength and/or quality that are not captured by DEXA assessment are abnormal in people with either type of diabetes and contribute to increased bone fragility. At present, there are no validated methodologies for assessing these aspects of bone quality. Several cross-sectional studies have evaluated bone microarchitecture in small numbers of people with type 2 diabetes using high-resolution computed tomography [226–230]. Four of five studies found similar bone structural variables between participants with and without type 2 diabetes, while one reported increased porosity of cortical bone at the radius but not the tibia in those with type 2 diabetes. In one study, microindentation analysis suggested a lower bone mechanical strength in the group with type 2 diabetes [228]. It therefore remains unclear whether abnormality of bone structure or quality exists in diabetes.

Potentially relevant to the notion that bone quality is impaired in diabetes is evidence that advanced glycation end-products (AGEs), products of non-enzymatic glycation, are present in greater amounts in the skeletons of diabetic animals than those of control animals [231]. The glycation of matrix proteins in bone may alter biomechanical properties in such a way as to decrease bone strength [232, 233]. *In vitro* studies suggest that AGEs inhibit differentiation of osteoblasts [231, 234] and increase differentiation of osteoclasts [235], thereby potentially altering bone remodelling and/or strength in a detrimental fashion. There may be AGE-specific effects on bone remodelling, as pentosidine decreases osteoclast development *in vitro* [236]. Mice deficient in the receptor for AGE exhibit increased bone mass and decreased osteoclast function, suggesting that the overall effect of increased AGE signalling in bone is likely to be detrimental [237]. A pivotal role for AGEs in the increased risk of fractures in diabetes implies that improved

glycaemia should ameliorate the risk. However, a secondary analysis of a randomized trial of intensive glycaemic management in type 2 diabetes did not find such an effect [238].

Finally, in type 2 diabetes there is clear evidence that treatment with either of the currently available thiazolidinediones, rosiglitazone and pioglitazone, increases fracture risk, at least in the appendicular skeleton in women [239, 240]. Data collected as adverse events during randomized controlled trials of each thiazolidinedione in middle-aged populations with type 2 diabetes demonstrated a twofold increase in risk of distal limb fractures in women, although not in men [241–243] (Figure 59.6). However, observational data from an older cohort of individuals with type 2 diabetes suggest that fracture risk is also increased in men exposed to thiazolidinediones, and that the incidence of *classic* osteoporotic fractures (hip, forearm, humerus) is also higher in thiazolidinedione users [244].

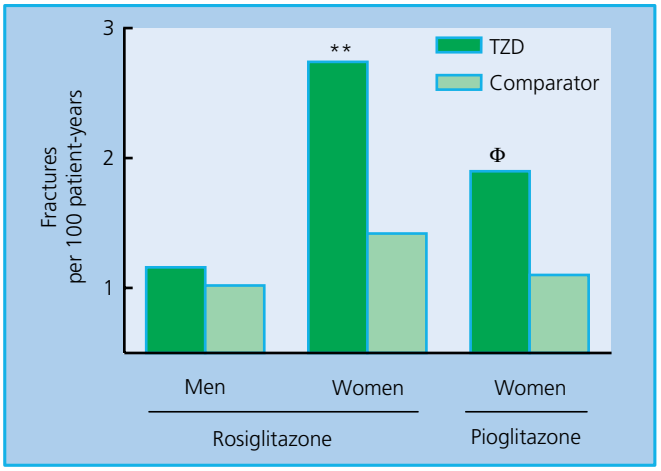

Figure 59.6 Fracture rates, captured as adverse events, in randomized controlled trials of thiazolidinedione (TZDs). **, $p<0.01$ vs comparator; φ, significantly higher than comparators. Source: Courtesy of A. Grey.

The mechanisms underlying the adverse skeletal effects of thiazolidinediones are complex and may involve both direct and indirect pathways (Figure 59.7). Of primary importance is the effect of the thiazolidinediones to directly inhibit bone formation, by diverting mesenchymal stem cell precursors from the osteoblast to the adipocyte lineage [239]. In addition, thiazolidinediones increase or maintain bone resorption at inappropriately elevated levels, via direct actions on osteoclast development [239, 245]. Indirect actions of thiazolidinediones that potentially contribute to their detrimental skeletal effects include decreasing systemic and skeletal production of IGF-1, modulating production of skeletally active adipokines, and decreasing levels of pancreatic β-cell hormones with known skeletal activity [240]. A substantial body of pre-clinical studies in rodents demonstrates that thiazolidinediones decrease bone formation and BMD *in vivo* [239]. In humans, randomized controlled trials have reported that thiazolidinediones reduce BMD over 12–18 months, although not markedly [246–249]. There was not a consistent pattern of changes in markers of bone turnover.

The skeletal toxicity of thiazolidinediones has prompted interest in the effects of other oral anti-diabetes agents on bone health. At present, the available data suggest that metformin, sulfonylureas, agents that modulate GLP-1 signalling, and SGLT-2 inhibitors are neutral in regard to the skeleton [250–253].

Investigation and management of osteoporosis in diabetes

Diabetes of either type should be regarded as a risk factor for fragility fracture, and included in clinical fracture risk assessment, along with recognized risk factors such as age, sex, body weight, previous fracture, cigarette smoking, glucocorticoid use, and BMD. Fracture risk algorithms assist in determination of an individual's short- to medium-term absolute fracture risk [190, 191], although they may underestimate risk in populations with diabetes [230]. Although BMD is on average increased in type 2 diabetes, measurement of BMD in people with type 2 diabetes is still helpful in defining that person's fracture risk. Prescription of thiazolidinediones to people with type 2 diabetes who are found to be at high risk of fracture should be avoided unless there are compelling reasons to do so.

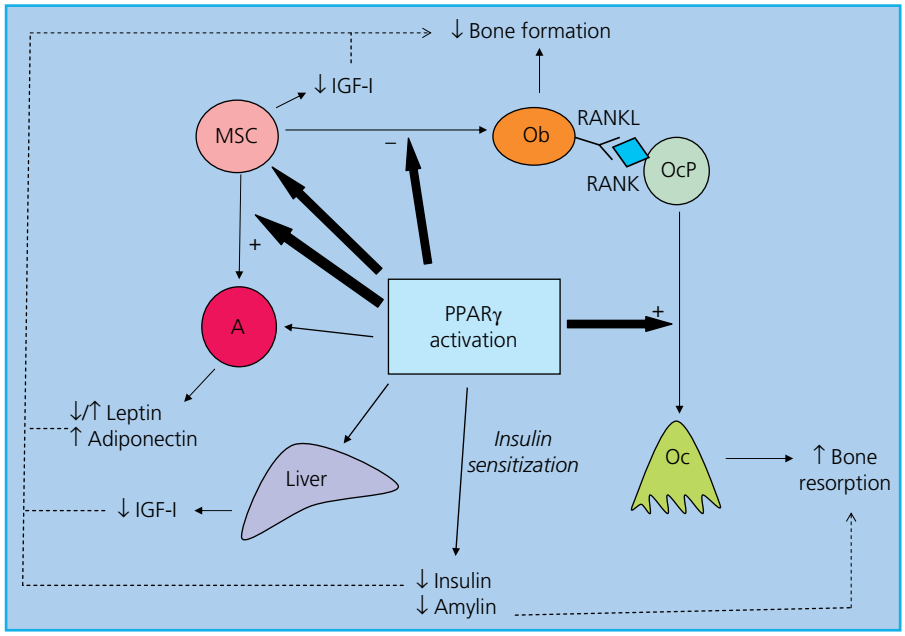

Figure 59.7 Mechanisms by which peroxisome proliferator-activated receptor (PPAR)γ regulates bone metabolism. Within the bone microenvironment (black arrows), activation of PPARγ signalling promotes differentiation of mesenchymal stem cells (MSC) into adipocytes (A) at the expense of osteoblasts (Ob), decreases stromal cell production of insulin-like growth factor (IGF)-I, and promotes differentiation of osteoclast precursors (OcP) into mature bone-resorbing osteoclasts (Oc). The net effect is to decrease bone formation and increase bone resorption. Activation of PPARγ signalling at extraskeletal sites such as adipose tissue and the liver, and the ensuing effects of insulin sensitization on the β cells of the pancreas (regular arrows), may have indirect impacts on the skeleton (interrupted arrows) by altering circulating levels of several hormones and cytokines, as indicated. RANK, receptor activator of NF-κB; RANKL, receptor activator of NF-κB ligand. Source: Courtesy of A. Grey.

Minimizing falls risk is an important component of skeletal management in diabetes; this can be achieved by targeting both macrovascular and microvascular disease complications, minimizing the risk of hypoglycaemia, optimizing visual acuity, and minimizing use of other medications known to be associated with falls. Although there are no data from interventional studies on the effects of pharmacological treatments on fracture risk in diabetes, it is reasonable to assume that agents known to prevent fractures in osteoporotic populations without diabetes, such as bisphosphonates, will also be effective in diabetes [188].

Fracture healing in diabetes

Some evidence suggests that fracture healing is abnormal in diabetes. In rat models of type 1 diabetes, the mechanical and structural properties of the healing bone are inferior in the diabetic rats when compared to control animals, findings that are accompanied by evidence of both decreased callus size and collagen content [254, 255]. Interventional studies demonstrate that insulin therapy to achieve normoglycaemia is associated with fracture healing that is indistinguishable from that observed in non-diabetic animals [256, 257]. Subsequently, administration of insulin at the site of skeletal injury was also shown to promote fracture healing, without altering serum glucose, implying a role for insulin in directly mediating bone repair [258]. Few data are available from human studies, but increased rates of fracture non-union in both type 1 diabetes and type 2 diabetes have been reported [259], as have higher than expected rates of serious complications in people with diabetes with open ankle fractures [260]. Diabetes is associated with a doubling of the risk of fracture-healing complications (delayed union, non-union, or malunion) [261], although long-term recovery might not be affected [262]. It is unknown whether interventions specifically targeted to populations with diabetes lead to improved post-fracture outcomes. Further investigation of the influence of diabetes and its treatment on fracture repair in humans is needed.

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60 Diabetes and Cancer: Risk, Outcomes, and Clinical Implications

Ellena Badrick[1], Emily J. Gallagher[2], and Andrew G. Renehan[1]

[1] Division of Cancer Sciences, University of Manchester, Manchester, UK

[2] Division of Endocrinology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Key points

- After accounting for confounding and biases, type 2 diabetes is causally associated with an increased risk of a limited number of types of adult cancer.
- In several Western countries, cancer is becoming the leading cause of death among people with diabetes as deaths from cardiovascular diseases decline.
- Two hypotheses seek to explain the pathophysiological mediation between diabetes and cancer risk, namely hyperglycaemia and hyperinsulinaemia.
- Earlier studies implicated several anti-diabetes drug classes in either increased (insulins, thiazolidinediones, incretin-based agents) or decreased (metformin) cancer risk. In hindsight, many of these earlier analyses overestimated the effect sizes. Updated reviews, using methods to reduce biases, generally weaken these associations.
- People with diabetes who develop cancer have a poorer response to treatment and reduced survival compared to those without diabetes.
- Research is needed to develop a better understanding of the interactions between diabetes, treatments, and treatment-related morbidity, and to determine whether there is a true (direct) adverse effect of diabetes on tumour biology in clinical practice.
- There are three major areas of clinical implication: cancer screening in diabetes; discussing cancer risk when commencing new anti-diabetes drugs; and the management of cancer treatment-related effects in individuals with diabetes.

Diabetes and cancer are common chronic conditions, and they frequently coexist. Worldwide, there were 4.6 million people with diabetes in 2019 [1] and 19.3 million people with new diagnoses of cancer in 2020 [2]. In the UK, it was estimated that 4.7 million people had diabetes in 2019, of whom ~1 million had undiagnosed type 2 diabetes [3]. Over the next 10 years, ~120 000 of these people will develop new cancer diagnoses (personal estimates). Estimates of co-occurrence of prevalent diabetes and cancer are age-, sex-, population-, and cancer type–specific but, for example, in the Danish population 35% will have a diagnosis of diabetes in their lifetime, 44% a diagnosis of cancer, and ~15% both diagnoses [4].

A link between diabetes and cancer was noted in print as early as 1914 [5], but diabetes–cancer associations were only glimpsed as secondary findings over the subsequent 80 years. However, in a 1991 paper focusing specifically on this link, using population data from Sweden, Adami et al. [6] noted significant increases in the risk of liver, endometrial, and pancreatic cancer among people with diabetes. In hindsight the occurrence of pancreatic cancer may in many cases reflect reverse causality; that is, the cancer causes metabolic changes that manifest themselves as symptoms of diabetes. This is now referred to as pancreatogenic diabetes or type 3c diabetes [7]. Interest in the diabetes–cancer link accelerated again in 2009, after four epidemiological studies evaluating links between cancer and diabetes therapies, in particular long-acting insulin analogues, were published simultaneously in *Diabetologia* [8]. The 2009 controversy brought together researchers from diabetes and oncology communities, and focused attention on the methodological complexities underpinning the links between diabetes and cancer [9].

This chapter will describe the epidemiological evidence evaluating associations between diabetes, cancer incidence, and mortality, and the emerging trends of cancer as a leading cause of death among people with diabetes. As a prelude, the challenge of epidemiological data interpretation is set out. The chapter then discusses the two prevailing mechanistic hypotheses linking diabetes and cancer, namely hyperglycaemia versus hyperinsulinaemia. The central tenet of anti-diabetes therapy is glucose management. From the pharmaco-epidemiological literature, there is evidence that anti-diabetes medications might influence cancer risk, but again, discussion is required around interpretation of these data. There is then a section on the impact of diabetes in individuals diagnosed with cancer. Here, there are additional complexities of treatment selection bias in the interpretation of the data. Finally, the chapter covers three major areas of clinical implication and the emergence of the subspecialty of *onco-diabetology*.

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Interpretation of the epidemiological evidence

Diabetes and cancer: potential confounding

A schematic representation of the causal mechanisms between diabetes and cancer risk is shown in Figure 60.1. Excess body weight or fatness, commonly expressed as elevated body mass index (BMI), is a mutual risk factor for the development of type 2 diabetes and for several cancer types [10], and it is conceivable that the positive associations between type 2 diabetes and cancer incidence may simply reflect excess body weight, or obesity, as a confounder. There are many pathophysiological mechanisms in obesity that are common to type 2 diabetes and may be important mediators of tumorigenesis [11]. These include alterations in sex hormone pathways, adipokines, and subclinical inflammation, hyperinsulinaemia, and aberrations in the insulin-like growth factor (IGF) system.

There are several justifications, however, to support the tenet that there are relationships between type 2 diabetes and cancer risk independent of BMI [12]. First, while the list of diabetes-related cancers and obesity-related cancers overlaps, there are some exceptions. For example, there are associations between diabetes and bladder cancer, but in general associations between obesity and bladder cancer are absent or very modest [13]. Another example is advanced prostate cancer, which is associated with an elevated BMI [11], while diabetes appears to be inversely associated with prostate cancer, at least in Western populations.

Second, cigarette smoking is a mutual risk factor for the development of both diabetes and several cancer types. Although this question is understudied, as few diabetes-related cancers are smoking-related cancers, it would seem that smoking is not a major confounder.

A note on ethnicity is pertinent. In the USA, compared with non-Hispanic white Americans (11%), the age-standardized prevalence of diabetes is higher among non-Hispanic Black Americans (22%), non-Hispanic Asians (21%), and Hispanic people (23%) [14], but cancer incidences are generally lower in the latter three ethnic groups compared with white populations. An exception is the incidence of prostate cancer, which is higher among non-Hispanic Black Americans compared with white populations.

Finally, cancer screening is an additional confounder; there might be differential rates of cancer detection between populations with and without diabetes if there were differential rates of cancer screening. For example, there are several trial-proven effective approaches to colorectal cancer screening, including faecal occult blood testing, once-only flexible sigmoidoscopy, and colonoscopy. There is some evidence [15] that people with type 2 diabetes underutilize colorectal cancer screening programmes. Similarly, women with diabetes have lower rates of attendance for mammographic screening for breast cancer than those without [15]. It is important to note that the risk estimates in Table 60.1 are relative (rather than absolute) risk. These are very modest elevated risks at an individual level and individuals with type 1 diabetes and type 2 diabetes do not require enhanced cancer screening.

Diabetes and cancer: potential biases

There are several specific biases important to the interpretation of the diabetes–cancer association, which include the following.

Detection time bias

This bias arises from the co-diagnosis of the disease exposure of interest (here, diabetes) and outcome of interest (here, cancer) in the same time window. Thus, there is a peak co-diagnosis of diabetes and cancer in the first 2–3 years after initial diagnosis of diabetes. However, these cancers diagnosed shortly after a new diagnosis of diabetes are generally not caused by diabetes. Inclusion of these cancers exaggerates the risk estimates for the diabetes–cancer associations (Figure 60.2). This co-diagnosis peak (and potential detection bias) is common for several cancer types after a new diagnosis of diabetes [18]. Some investigators refer to this as protopathic bias [19], and argue that it is a serious cause of inflated risk estimates between diabetes and cancer incidence. Within the co-diagnosis peak, there are at least three underlying causal relationships: reverse causality; heightened clinical investigations (ascertainment bias) from diabetologists; and heightened clinical investigations from the oncology team. The simple methodological solution is to use an incident diabetes cohort and exclude cancers diagnosed in the first 2–3 years. An alternative solution is to use time-varying hazard models, as shown in Figure 60.2.

Immortal time bias

This refers to a period of follow-up during which, by design, death or the study outcome cannot occur [20]. This bias is common and well known in the pharmaco-epidemiology literature, but not always appreciated in the general clinical epidemiology literature. In pharmaco-epidemiology studies, immortal time typically arises when the determination of an individual's treatment status involves a delay or wait period during which follow-up time is accrued. This wait period is considered immortal because individuals who end up in the treated or exposed group have to survive until the exposure definition is fulfilled, for example at least two prescriptions of an anti-diabetes therapy. If they have an event before starting treatment, they are placed in the untreated or unexposed group. Immortal time bias is particularly problematic because it biases the results in favour of the treatment under study by conferring a spurious survival advantage to the treated group (a misclassification

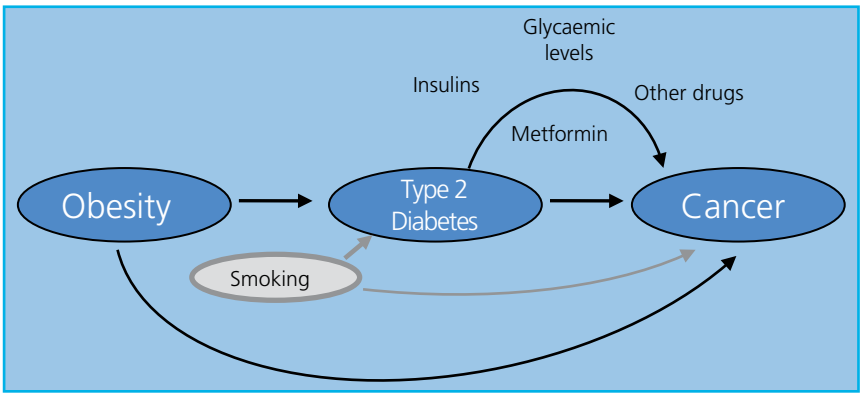

Figure 60.1 Schematic representation of the complexities of the link between obesity, diabetes, and cancer. Obesity is a mutual risk factor for type 2 diabetes and cancer, and might confound the relationship between diabetes and risk of incident cancer. Smoking is another potential mutual risk factor, though less well studied.

Table 60.1 Summary estimates from two large meta-analyses of risk of incidence cancers in populations with type 2 diabetes.

	Tsilidis et al. 2015 [16][a]				Ling 2020 et al. [17]		
Cancer type	**No. of studies**	**Summary risk estimates (95% confidence intervals)**	**I^2**	**Summary risk estimates (95% prediction intervals)**	**No. of studies**	**Summary risk estimates (95% confidence intervals)**	**Evidence for causal association**
Hepatocellular carcinoma	42	2.31 (1.87 to 2.84)	97%	(0.66 to 8.02)	36	**2.23 (1.99 to 2.49)**	In bias analyses the proportion of studies with a true effect size larger than a risk ratio (RR) of 1.1 was nearly 100% for liver, pancreatic, and endometrial
Intrahepatic cholangio-carcinoma	9	1.97 (1.57 to 2.46)	54%	**(1.11 to 3.49)**		Not included	
Extrahepatic cholangio-carcinoma	9	1.63 (1.29 to 2.05)	64%	(0.86 to 1.95)		Not included	
Endometrial cancer	21	1.97 (1.71 to 2.27)	60%	**(1.23 to 3.16)**	15	**1.63 (1.41 to 1.88)**	
Pancreatic cancer	35	1.95 (1.66 to 2.28)	94%	(0.87 to 4.34)	38	**2.09 (1.88 to 2.33)[b]**	
Gallbladder cancer	11	1.52 (1.26, to .84)	32%	(0.99 to 2.33)	17	1.61 (1.34 to 1.93)	[c]
Renal cancer	18	1.38 (1.10 to 1.72)	93%	(0.55 to 3.44)	23	1.32 (1.21 to 1.44)	[c]
Bladder cancer	36	1.35 (1.17 to 1.56)	95%	(0.61 to 3.02)	20	1.19 (1.09 to 1.29)	
Oesophagus cancer	17	1.30 (1.12 to 1.50)	41%	(0.86 to 1.95)	19	1.01 (0.89 to 1.15)	
Leukaemia	11	1.28 (1.05 to 1.57)	89%	(0.66 to 2.48)	12	1.19 (1.07 to 1.31)	[c]
Colorectal cancer	30	1.27 (1.21 to 1.34)	48%	**(1.07 to 1.52)**	47	1.29 (1.23 to 1.36)	
Non-Hodgkin's lymphoma	21	1.27 (1.09 to 1.48)	85%	(0.70 to 2.30)	12	1.17 (1.09 to 1.31)	
Multiple myeloma	10	1.27 (0.98 to 1.64)	85%	(0.56 to 2.86)		Not included	
Melanoma		Not included		Not included	11	1.06 (0.95 to 1.19)	
Breast cancer	20	1.20 (1.12 to 1.28)	48%	**(1.01 to 1.43)**	32	1.10 (1.05 to 1.15)	
Ovarian cancer	18	1.17 (1.02 to 1.34)	41%	(0.79 to 1.72)	20	1.14 (1.03 to 1.26)	
Thyroid cancer	8	1.16 (0.97 to 1.39)	0%	(0.93 to 1.45)	14	1.20 (1.12 to 1.29)	
Gastric cancer	21	1.09 (0.98 to 1.22)	81%	(0.72 to 1.65)	28	1.19 (1.05 to 1.35)	
Lung cancer	24	1.03 (0.94 to 1.13)	95%	(0.70 to 1.52)	32	1.05 (0.99 to 1.12)	
Prostate cancer	45	0.91 (0.82 to 1.01)	95%	(0.49 to 1.69)	39	0.83 (0.79 to 0.88)	

Estimates in bold are considered to be causal.

[a]Tsilidis et al. [16] used assessment of between-study heterogeneity (I^2), assessment of small study effects, and evaluation of excess significance to interpret their data, and reported 95% prediction intervals in addition to the traditional reporting of 95% confidence intervals. I^2 values greater than 50% indicate a high level of between-study heterogeneity.

[b]It is unclear when reverse causality was taken into account properly in the meta-analysis.

[c]In bias analyses, assuming an unmeasured confounding associated with both type 2 diabetes and cancer with an RR of 1.5, the proportion of studies with a true effect size larger than an RR of 1.1 (i.e. 10% increased risk in individuals with type 2 diabetes) was 86% for gallbladder, 67% for kidney, 64% for colon, 62% for colorectal, and <50% for other cancer incidences.

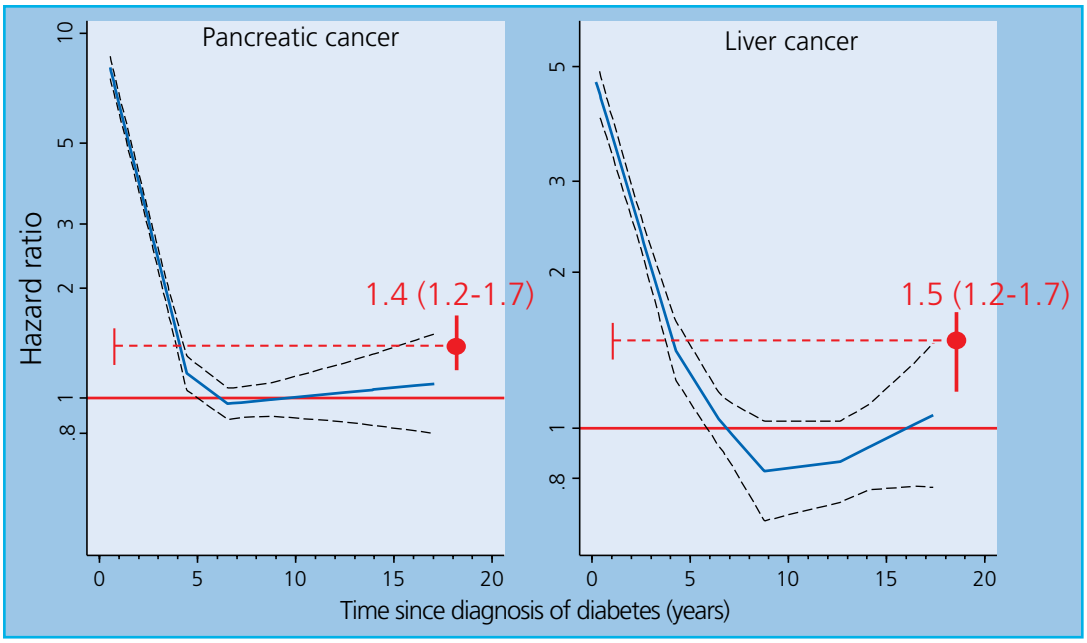

Figure 60.2 Detection time bias. This bias arises due to the co-diagnosis in time of the disease exposure of interest (here, diabetes) and outcome of interest (here, cancer). The hazard plots here are based on data from Adami et al. 1991 [6] and show how the hazard varies with time since diagnosis of diabetes, shown for pancreatic and liver cancers. There is a peak co-occurrence of diabetes and cancer in the first 2–3 years. However, these cancers are not caused by diabetes. If we include these cancers in the risk association model (fixed-cohort analysis, shown as a red dotted line), the net risk estimates are 1.4 and 1.5, respectively, and 95% confidence intervals (CIs) are greater than 1, suggesting a significant positive association. However, in the preferred time-varying model (shown as a blue line, 95% CIs, and grey dotted lines), the hazard between 5 and 15 years after diabetes diagnosis is close to 1; that is, a null association. It is only 15 years after diabetes diagnosis that there is a suggestion of a positive 'causal' association between diabetes and risk of pancreatic and liver cancers.

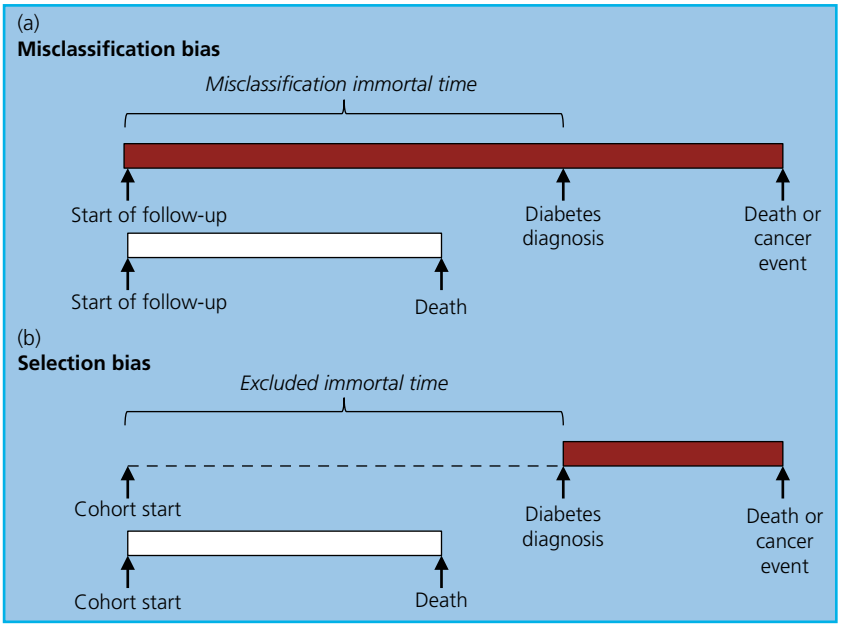

Figure 60.3 Immortal time bias is introduced in cohort studies when the period of immortal time is either (a) incorrectly attributed to the treated group through a time fixed analysis or (b) excluded from the analysis because the start of follow-up for the treated group is defined by the start of treatment and is, by design, later than that for the untreated group. Source: Modified from Levesque et al. 2010 [21].

bias); and because, by excluding the survival time in people who later take up the treatment, the survival time of the narrowly defined non-treatment group is disadvantaged (selection bias; Figure 60.3). These principles can be readily extended to diabetes as the exposure and incident cancer as the event of interest. Immortal time bias should be suspected in fixed-cohort analyses where the covariate diabetes is handled as an *ever/never* term. A methodological solution is to use time-varying models [21, 22].

Allocation bias

This is particularly prevalent in pharmaco-epidemiological studies and is sometimes referred to as confounding by indication, where for example insulin therapy is generally prescribed late in the course of diabetes when individuals are older and *sicker*. Unsurprisingly, these biases result in an apparent increased cancer risk [23]. Methodological solutions require advanced methods such as inverse probability weighting and modelling the data with two time-updated terms in the model [24].

Survival bias

This bias is due to differential survival (or differential loss to follow-up) in individuals undergoing the index exposure (here, diabetes or diabetes therapies) compared with that of the comparator group. In turn, this will differentially influence the number of individuals at risk to developing the index event of interest (here, subsequent incident cancer). This is sometimes referred to as susceptibility bias, and is a specific form of selection bias. The methodological solution here is to use competing risk analyses.

Diabetes and cancer risk: epidemiological evidence

Cancer incidence

In this chapter of the 2017 edition of this textbook, we summarized a large volume of epidemiological evidence evaluating associations between diabetes and cancer risk, and concluded that diabetes may be independently associated with many different types of cancer [25]. That perception is changing in recent years, as indicated in two large reviews. One was an umbrella review reported by Tsilidis et al. [16] based on 18 meta-analysis papers (27 independent meta-analyses from 474 individual studies) and the other was reported by Ling et al. [17] based on 151 cohorts and incorporating over 32 million people and 1.1 million cancer cases. Both reviews used novel methods to take account of the likely confounding and many biases assumed to be operating in many previous meta-analyses. Specifically, Tsilidis et al. [16] used assessment of between-study heterogeneity, assessment of small study effects, and evaluation of excess significance to interpret their data. Additionally, they reported 95% prediction intervals as well as the traditional reporting of 95% confidence intervals. By contrast, Ling et al. [17] employed a bias analysis for unmeasured confounding, quantifying the proportion of studies with a scientifically meaningful effect size; that is, a true effect size above a pre-specified relative risk.

Table 60.1 summarizes the relative risks per cancer type for each of these two reviews. Applying the methodological frameworks just outlined, Tsilidis et al. [16] concluded that 'evidence could be substantiated only for the associations between type 2 diabetes and risk of developing breast, intrahepatic cholangiocarcinoma, colorectal, and endometrial cancer'. Similar, Ling et al. [17] arrived at a short-list, reporting that their findings 'strongly suggest a causal association between type 2 diabetes and liver, pancreatic, and endometrial cancer incidence'.

Type 1 diabetes and cancer risk

Whether there is a link between type 1 diabetes and cancer risk is not always readily answered, as studies often do not distinguish between type 1 diabetes and type 2 diabetes, and reviews on this question yield mixed results [26]. As type 1 diabetes presents in childhood, very long-term follow-up is required to detect sufficient numbers of common adulthood epithelial cancers for meaningful association analyses. Probably for this reason, when some shorter-term studies address this question, they tend to find increases in the risk of malignancies of early adulthood, such as lymphoma [27].

Large cohorts of people with type 1 diabetes are now surviving into their middle and late adulthood. A recent collaborative

analysis from five countries identified 8800 cancers in individuals with type 1 diabetes followed for 3.7 million person-years, and reported that the pattern of increased incident cancer types mirrors that for type 2 diabetes [28]. However, overall the effect sizes are very modest and smaller than those for type 2 diabetes and cancer risk. As all these individuals are on long-term insulin therapy, this study concluded that they could not exclude an effect from this medication.

Gestational diabetes and cancer risk

Women with gestational diabetes are a readily identifiable population of young women with early evidence of glucose dysregulation and insulin resistance, and are at high risk of subsequently developing diabetes and cardiovascular disease. Glucose intolerance subsides in the majority of women after delivery, but may persist. There are studies suggesting positive associations between gestational diabetes and later breast, ovarian, and uterine cancers [29], while others show no associations [30]. There are many potential confounders in these relationships, which might influence in complex directions. While pre-pregnancy obesity, number of pregnancies, and age are all risk factors for gestational diabetes, early adulthood obesity is relatively protective for postmenopausal breast cancer [31]. One Canadian group attempted to address some of these complexities in a matched study design of nearly 50 000 women with gestational diabetes and found no association between gestational diabetes and premenopausal breast cancer [32].

Diabetes and cancer mortality: evidence

Cancer mortality

Again, in this chapter of the 2017 edition of this textbook, we concluded that associations between diabetes and cancer-related mortality are broadly consistent with those for cancer incidence [25]. Similar to cancer incidence, recent evidence indicates that a revised conclusion should be considered. The Tsilidis umbrella review [16] reported summary estimates for cancer-related mortalities from the breast, colorectum, endometrium, stomach, liver, and kidney. In all these, there was considerable heterogeneity between studies with resulting wide prediction intervals, such that the authors concluded that 'none of the associations for mortality passed our assessment for robust associations without evidence of bias'. By contrast, the authors of the Ling review [17] concluded that their findings 'strongly suggest a causal association between type 2 diabetes and pancreatic cancer mortality'.

At a public health level, the mortality data are helpful as an index of disease burden. However, at a clinical level there are limitations, as mortality from cancer is conditional on the occurrence of cancer, such that these studies fail to disentangle the impact of diabetes on incidence versus treatment outcome, treatment-related morbidities, and impact of type 2 diabetes on quality of life in individuals with cancer.

Cancer as the leading cause of death in diabetes

In 2014, an Australian study reported on trends in causes of death in over 1.1 million people with diabetes between 1997 and 2010, noting that cardiovascular disease is the commonest contributor to death but has declined [33]. By contrast, cancer deaths have increased and have become the second commonest contributor to death. More recently, Pearson-Stuttard et al. [34] evaluated trends in predominant causes of death in over 300 000 individuals with diabetes in England (2001–2018). They concluded that 'the decline in vascular death rates has been accompanied by a diversification of causes in individuals with diagnosed diabetes and a transition from vascular diseases to cancers as the leading contributor to diabetes-related death'. Similarly, trend data on causes of death from the Swedish National Diabetes Registry predict that cancer will be the leading cause of death among individuals with type 2 diabetes by 2030 [35].

Hyperglycaemia and hyperinsulinaemia in cancer

Metabolic derangements underlie the development of type 2 diabetes and these have been proposed to contribute to cancer development and progression [36]. Here we will examine two theories: the hyperglycaemic and hyperinsulinaemic hypotheses [37].

Hyperglycaemia is the clinical hallmark of diabetes and could be a major risk factor for cancer development [38]. Pre-diabetes, which is defined by glucose excursions above what is considered the normal range but not yet meeting the criteria for type 2 diabetes, is also associated with an increased risk of cancer [39]. In clinical practice, a radiolabelled glucose analogue (^{18}F-fluorodeoxyglucose) is frequently used to detect cancer by positron emission tomography–computed tomography (PET-CT) imaging, due to the known characteristic of certain cancer cells to take up more glucose than non-cancer cells [40]. This phenomenon is related to their high rates of glycolysis relative to normal cells, first recognized by Otto Warburg, who received the Nobel Prize in Physiology or Medicine in 1931.

It is conceivable that hyperglycaemic conditions provide more fuel to cancer cells and facilitate a relative growth advantage. However, most cancer cells express glucose transporters that have a constitutively high level of glucose uptake, and are able to fully satisfy their glucose requirements under normoglycaemic conditions [41]. *In vitro* studies have reported increased proliferation of breast and pancreatic cancer cell lines in high-glucose (25 mmol/l) compared with low-glucose (5.5 mmol/l) conditions. In addition, high-glucose conditions lead to molecular changes within cancer cells and the tumour-associated microenvironment, such as alterations in signalling pathways, greater production of reactive oxygen species, promotion of angiogenesis, and epithelial-to-mesenchymal transition. These molecular changes contribute to cancer cell growth, metastasis, and resistance to treatment [42].

Some population-based studies reported a dose–response relationship between glucose concentration and the incidence and mortality from pancreatic cancer across the pre-diabetes and diabetes range of glucose levels [43]. There is also some population-level evidence that high glycated haemoglobin (HbA_{1c}) is related to the incidence and mortality of some cancers [44], although not all studies have replicated these findings [45]. Interestingly, in US and European cohorts, the duration of diabetes was not associated with cancer risk [46]. Anti-diabetes therapy does not appear to diminish the risk of cancer in people with diabetes. For example, a meta-analysis of major trials examining intensive glycaemic management and cancer risk concluded that it is unlikely hyperglycaemia plays a role in cancer development [47]. Further evidence comes from data comparing anti-diabetes therapies and categorizing drugs that increase insulin levels (exogenous insulin or secretagogues) and

drugs that lower insulin levels, such as metformin and thiazolidinediones. If within-drug groups are stratified by glycaemic levels, no difference is observed by HbA_{1c} status. This evidence would dispute the hyperglycaemia theory [48]. These findings on cancer risk contrast with the risk of microvascular complications associated with diabetes, where longer diabetes duration increases the risk, which can be mitigated by treatment to reduce HbA_{1c} levels.

While measures of hyperglycaemia (glucose or HbA_{1c}) are the clinical biomarkers used to diagnose type 2 diabetes, endogenous hyperinsulinaemia is present for many years before hyperglycaemia develops, and has been associated with cancer risk and progression in population-based studies [49]. Insulin resistance was classically thought to be the cause of hyperinsulinaemia, but now it is appreciated that hyperinsulinaemia contributes to the development of insulin resistance [50]. Using the UK Biobank, a Mendelian randomization study found that genetically predicted fasting insulin levels were positively associated with uterus, kidney, pancreas, and lung cancers [51]. In women with early-stage breast cancer, fasting insulin levels are associated with worse outcomes [52].

Pre-clinical studies have found that hyperinsulinaemia contributes to tumour development and progression by enhancing the survival of cells that have acquired mutations, by increasing cell proliferation, and by promoting epithelial-to-mesenchymal transition [49, 53]. Cancer cells express a mitogenic form of the insulin receptor (IR-A) that is also expressed in fetal tissues, as well as the type 1 insulin-like growth factor receptor (IGF-IR). Hyperinsulinaemia may therefore directly act on tumour cells through IR-A, or may have indirect effects on cancer cells by increasing the bioavailability of IGF-I, which may activate the IGF-IR [49]. Insulin resistance may also promote cancer growth by altering the tissues and cells in the tumour microenvironment, including tumour-associated adipose tissue and immune cells. Systemically, insulin resistance is associated with decreased sex hormone–binding globulins leading to excess bioavailable oestrogen, dyslipidaemia with higher production of non-esterified fatty acids and other bioactive lipids, and higher levels of pro-inflammatory cytokines and adipokines [11]. Notably, cancers are heterogeneous and insulin responsiveness is not universal. Nonetheless, the accumulation of experimental and epidemiological evidence is consistent with a hyperinsulinaemia hypothesis, and hyperinsulinaemia may have synergistic effects with hyperglycaemia and other metabolic factors associated with insulin resistance to drive tumorigenesis.

Pharmaco-epidemiology: anti-diabetes agents and cancer risk

Interpretation

All the confounding and biases described, in relation to the interpretation of epidemiological studies evaluating diabetes and cancer risk, apply to the pharmaco-epidemiology of anti-diabetes therapies and cancer risk. These concerns have been addressed in a concept paper from the Diabetes and Cancer Research Consortium (DCRC), an international group mainly focusing on pharmaco-epidemiological queries in the complex relationships between diabetes, diabetes treatment, and cancer risk [23]. In this framework document, two important methodological features were emphasized: the need to account for detection time bias; and the need to set up data to account for time-varying exposures, namely immortal time bias. The interpretations of many early 'first-generation' reports were limited by failure to take account of these key analytical issues [22].

Additionally, allocation bias deserves specific comment, here in relation to the pharmaco-epidemiology of anti-diabetes drugs and cancer risk. To address this bias, one solution advocated by the DCRC group is to model the data with two time-updated terms in the model: a binary term for ever exposure up to that time point; and a continuous term for cumulative exposure [24]. Further methodological work from DCRC members came when Walker and colleagues [54], who summarized the problems of capturing drug exposure from observational datasets and described optimal methodology to reduce bias. For instance, they illustrated that different anti-diabetes drugs are administered as type 2 diabetes progresses, making direct *trial-like* comparisons between drug classes uninterpretable. In this setting, the use of ever/never drug exposure categories only should be avoided, and cumulative exposure handled statistically as a time-varying covariate. We have referred to studies that use these methodologies as *second generation* [22]. These points are worth remembering when reading the next sections.

Anti-diabetes drugs and cancer risk

In this chapter in the 2017 edition of this textbook [25], we catalogued potential relationships between many anti-diabetes drug classes and cancer risk. At that time, there were residual concerns around insulin therapies, particularly long-acting insulin analogues, and increased cancer risk. There were extended concerns that other drug classes that enhanced insulin secretion might also carry these risks. Many of these concerns have subsided or at least been attenuated. They are summarized in Table 60.2 using data from various updated reviews and meta-analyses covering all anti-diabetes drugs [56, 57, 64] or selective drug classes, such as thiazolidinediones [58], α-glucosidase inhibitors [59], incretin-based drugs [60, 61], and sodium–glucose cotransporter 2 (SGLT-2) inhibitors [62, 63]. Here, we will limit the discussion to cancer risk associated with metformin, insulin, and pioglitazone.

Metformin and cancer risk

For over a decade, there have been suggestions in the epidemiological literature that, among people with type 2 diabetes, use of metformin is associated with a reduced risk of certain cancers [65]. Coupled with these observations, there are now many laboratories across the globe exploring the role of metformin in cancer, and several novel anti-cancer mechanisms have been demonstrated and validated, beyond its well-known clinical anti-diabetes effects [66]. Many oncology trials are now being developed to test metformin as a repurposed, inexpensive licensed drug with a potential anti-cancer effect in the clinic [67].

However, we now understand that many of the earlier epidemiological studies on this question contained time-related biases that artificially made metformin look *protective*. Most important of these was immortal time bias. The net result of this bias is an advantage to the users of the drug of interest (here, metformin) when the analysis is simply categorized by ever/never use. This was well illustrated by Suissa et al. [68], who found that immortal time bias was prevalent among many studies that reported a reduced cancer risk associated with metformin use. By contrast, those studies that used methods to avoid these biases reported no effect of metformin use on cancer incidence.

A more recent study by Farmer and colleagues [69] recognized that when studying time-varying exposure to metformin, covariates such as BMI and HbA_{1c} may act as both confounders and

Table 60.2 Summary of evidence evaluating anti-diabetes medications and cancer risk.

Drug class	Plausible cancer mechanism	Drug subclass	Summary risk estimates	Interpretation
Insulin	Increase in cell proliferation Anti-apoptotic Associated with weight gain May mimic insulin-like growth factor I (IGF-I)	Long-acting insulin analogues	CARING five-country cohort study (327 112 new insulin users) [55]: 'No evidence of consistent differences in risk for 10 cancers for insulin glargine or insulin detemir use compared with human insulin, at follow-up exceeding 5 years'	In well-designed analyses taking account of immortal time bias, there appears to be no increased risk between long-acting insulin analogues and cancer incidence
Insulin secretagogues	Enhances β-cell insulin secretion Associated with weight gain	Sulfonylureas	All cancers: meta-analysis of 72 studies found a 20% increased cancer risk [56]. High level of heterogeneity. Sub-meta-analysis of 38 randomized controlled trials (RCTs) found no association with cancer risk [56]	In analyses that take account of selection bias, there appears to be no increased risk between insulin secretagogues and cancer incidence
		Meglitinides	Meta-analysis of 8 studies found no association between meglitinide use and all-site cancer risk [56]	
Metformin	Metformin inhibits mitochondrial complex I, decreasing the adenosine monophosphate (AMP)/adenosine triphosphate (ATP) ratio and deactivating the energy sensor AMP-activated protein kinase (AMPK), in turn reducing blood glucose, hyperinsulinaemia, and IGF-I These may be indirect effects in cancer protection	Metformin	See main text for methodological time-related biases in pharmaco-epidemiology studies of metformin use and cancer risk Three studies (cited in [57]), attempting to account for time-related biases, particularly by comparing new users of metformin and sulfonylureas, did not find evidence for a protective effect of metformin	There is much written on the potential anti-cancer effects of metformin The main text summarizes the many potential methodological flaws Nonetheless, there are now several trials in the setting of cancer evaluating the many hypothesized benefits of metformin; results awaited.
Thiazolidinediones	Thiazolidinediones are insulin sensitizers acting via the peroxisome proliferator activated receptor-γ (PPAR-γ), inducing insulin secretion and improving insulin sensitivity	Pioglitazone	See main text for bladder cancer risk controversy in 2016 All cancers: a meta-analysis of 92 RCTs showed no association of thiazolidinediones with all-site cancer [56]	The finding for thiazolidinediones are often mixed RCTs in this field may be useful to reduce treatment selection bias, but they suffer from short follow-up and post-randomization selection biases
		Rosiglitazone	A meta-analysis of 22 RCTs reported a significant reduction in the incidence of malignancies including rosiglitazone, but not pioglitazone, with reduced colorectal cancer risk; and an association of pioglitazone, but not rosiglitazone, with a reduced breast cancer risk [58]	
α-Glucosidase inhibitors	Increases plasma glucagon-like peptide 1 (GLP-1) levels Weight loss	Voglibose Miglitol Acarbose	A meta-analysis of four RCTs found no association with cancer risk [59]	Appears to be no association with cancer risk
Incretin-based drugs	Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) mimic the action of endogenous GLP-1 Delay gastric emptying Enhance glucose homeostasis through stimulation of insulin secretion and inhibit glucagon secretion	Dipeptidyl peptidase 4 (DPP-4) inhibitors	Early report from US Food and Drug Administration database (2004–2009) showed an increased prevalence of pancreatic cancer among users of the DPP-4 inhibitor sitagliptin and the GLP-1 mimetic exenatide A Cochrane review (including 13 studies comparing DPP-4 inhibitors with placebo) concluded that the quality of evidence was too low to determine an effect of DPP-4 inhibitors on pancreatic cancer [60] All cancers: a meta-analysis of 72 RCTs found no association between DPP-4 inhibitors and increased cancer risk [61]	There is a link between incretin-based drugs and pancreatitis, and this might be a confounder for pancreatic cancer risk evaluation
		GLP-1RAs	A meta-analysis of 14 RCTs reported no association of GLP-1RAs with cancer risk [56].	
Sodium–glucose cotransporter 2 (SGLT-2) inhibitors	Increased urinary excretion of glucose	All SGLT-2 inhibitors	A meta-analysis of 27 RCTs found no association with bladder or other cancers [62] A meta-analysis of 21 RCTs (n = 20 308 on SGLT-2; median follow-up 52 wk) concluded that SGLT-2 inhibitors are associated with increased risk of skin cancers [63]	No evidence for association, but follow-up is very limited
		Dapagliflozin	A meta-analysis of 7 studies (n = 27 744 on SGLT-2; follow-up at least 52 wk) found no association with cancer [56]	No evidence for association, but long-term follow-up not captured

causal pathway variables, and so cannot be handled adequately by standard (statistical) regression methods. Using primary care data from the UK Clinical Practice Research Datalink (CPRD), they built marginal structural models with inverse probability of treatment weightings, which can correctly adjust for such confounders. They found no protective effect on metformin on cancer.

Second, treatment allocation bias is a potential pitfall to interpretation. For example, metformin is first-line treatment for diabetes, and is therefore used earlier in the disease course than other medications. Those who reach glucose targets with metformin alone differ in disease severity from those who require additional medication. Differential allocation of drugs based on such confounding factors tends to exaggerate the protective benefits of metformin. Differential allocation is an inevitable bias in observational studies and has to be addressed within a randomized trial framework.

The third key appreciation in the story of metformin and cancer lies in the biology. It has become clear that many pre-clinical studies use concentrations of metformin higher than those safely obtained in the clinical setting. Most *in vitro* studies report using doses of metformin between 1 and 40 mM, which is well above the feasible therapeutic plasma levels (0.465–2.5 mg/l or 2.8–15 mmol/l) in humans [70]. It is possible that metformin causes an energy stress in these studies that far exceeds effects seen clinically.

Insulins and cancer risk

There are hypothetical physico-chemical reasons why some insulins might be pro-tumorigenic. Specifically, molecular engineering of the insulin molecule to form insulin analogues results in a molecule that *looks* more like IGF-I, with high affinity for the IGF-IR [71] (Figure 60.4). This receptor and its downstream pathway are important for tumour development.

In the late 2000s, several observational studies evaluated the putative link between insulin glargine and cancer risk, and were subsequently meta-analysed in several reviews [72]. In general, there are many inconsistencies in the findings of these meta-analyses. In turn, these reflect important design differences in the included studies. For example, some studies evaluated any insulin use versus non-insulin therapies in people with diabetes, while others evaluated glargine versus non-glargine insulin use. As insulin is generally prescribed late in the course of diabetes, individuals are older and *sicker*, and not surprisingly these biases result in an apparent increased cancer risk. None of the meta-analyses directly addressed the problem of time-related biases. For similar reasons, lumping data from case–controls (where time-varying exposures generally cannot be modelled) with cohorts is problematic.

The publication of the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial in 2012 brought some clarity to these inconsistencies. This trial randomly assigned 12 537 individuals with impaired glucose tolerance or type 2 diabetes to receive insulin glargine versus standard care in the largest trial of its type [73]. Although the protocol endpoints were cardiovascular non-fatal events or deaths, following concerns emerging about cancer links in the late 2000s, the investigators additionally detailed risk per cancer type by treatment allocation. Although follow-up was relatively short (median 6.2 years), the study concluded that there were no differences between treatment arms for all cancer incidence or deaths, and no differences between treatment arms for specific reported cancer types.

In 2017, a large consortium of national databases from five northern European countries, known as the CAncer Risk and INsulin analoGues (CARING) study [55], assembled over 327 000 new insulin users. Using second-generation study methodologies, it found no consistent signal of increased cancer risk associated with insulin use, and there were no differences between glargine or detemir long-acting insulin analogues.

Pioglitazone and bladder cancer risk

Pioglitazone and rosiglitazone are thiazolidinediones, which act as peroxisome proliferator-activated receptor-γ (PPARγ) agonists and are used as second-line therapies in the treatment of type 2 diabetes. Their use has been questioned owing to safety concerns because in pre-clinical studies, exposure of male rats to pioglitazone was associated with an increased risk of bladder cancer. In 2005, the prospective pioglitazone clinical trial in macrovascular events (PROactive, a large European randomized controlled trial evaluating the effects of pioglitazones on cardiovascular outcomes) found a non-significant increase in the incidence of bladder cancer in the pioglitazone-treated group. Based on these animal studies and trial data, the US Food and Drug Administration (FDA) commissioned the manufacturer to carry out a 10-year observational cohort study to examine this risk further. An initial mid-term analysis showed that two or more years of cumulative exposure to pioglitazone were associated with an increased risk of bladder cancer [74]. Around the same time, a similar increase in risk was observed in a French cohort [75], which led to the withdrawal of pioglitazone from France and Germany.

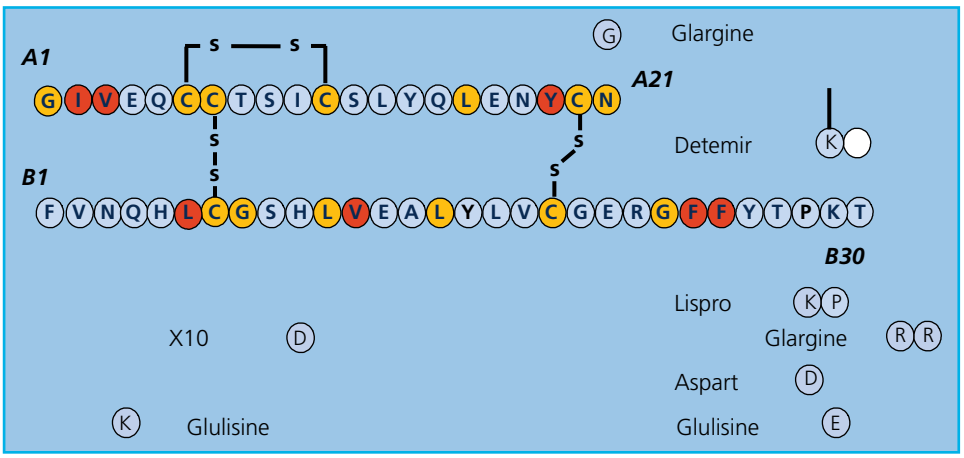

Figure 60.4 Schematic representation of molecular engineering of the insulin molecule. Most of the engineering is in the B-chain, except for glargine, which is an amino acid substitution in the A-chain. These molecular changes make insulin more insulin-like growth factor I (IGF-I) *like*. The net results are twofold: increased affinity for the mitogenic IGF-I receptor (IGF-IR) and slower dissociation time off the IGF-IR. Source: Modified from Kaarsholm et al. 1995 [71].

More recently, two large analyses report a lack of association between pioglitazone and bladder cancer. Levin et al. [24], on behalf of the DCRC, performed an international (six populations) cumulative exposure analysis on 1.01 million people with diabetes with 3248 incident bladder cancers. Lewis et al. [76] explored associations between pioglitazone use in people with diabetes and incident bladder cancer in a 10-year follow-up of a Kaiser Permanente Northern California (KPNC) cohort (193 099 persons, 1261 bladder cancers). Both analyses found no associations between pioglitazone use and incident bladder cancer risk. An additional study from the KPNC group indicated that proteinuria testing in people with diabetes may be a confounder in studies of pioglitazone and bladder cancer [77].

Impact of diabetes on outcome after cancer diagnosis

While the link between diabetes and incident cancer risk is now established, it is less clear, and indeed more complex, to interpret whether diabetes at or after cancer diagnosis has an adverse impact on outcome. Generally, there are two distinctive study designs: inception cohort studies that evaluate the effect of baseline diabetes on cancer-related mortality in general populations; whereas the oncology literature often uses cohorts of people with a cancer diagnosis and pre-existing type 2 diabetes and evaluates the endpoints of cancer-specific survival (or mortality). Some epidemiologists refer to the latter as case fatality studies. The clinical implications of the findings from these study types differ considerably: in statistical terms, time zero is at baseline cohort entry in the former, whereas time zero is date of cancer diagnosis or cancer initial treatment in the latter.

Within the two study designs, there are multiple levels of potential confounding and biases of cancer morbidity and mortality studies. A methodological group of the DCRC has identified nine levels on the cancer pathway at which confounding may arise [15]: cancer screening use; stage at diagnosis; cancer treatment selection; cancer treatment complications and failures; peri-treatment mortality; competing risks for long-term mortality; effects of type 2 diabetes on anti-cancer therapies; effects of anti-diabetes treatments on cancer outcome; and differences in tumour biology.

In the face of these limitations, the current evidence on the impact of diabetes on outcome after cancer diagnosis is as follows:

- Diabetes is associated with increased all-cause mortality in individuals with cancer, but the evidence that it influences cancer-specific mortality is inconsistent [15].
- For some cancers, there is evidence that people with type 2 diabetes present with more advanced disease, receive suboptimal treatment, and have poorer oncological outcomes [78].
- Compared with individuals with cancer but without diabetes, people with cancer and diabetes have a poorer quality of life and reduced physical activity [79].

While diabetes negatively affects survival, it is unclear whether the presence of diabetes in individuals with cancer has an adverse impact on prognosis above and beyond that expected in a non-cancer (general) population. In other words, is there a diabetes–cancer interaction? Simulation studies indicate that it is plausible to have a scenario where cancer survivors with diabetes have a worse survival than those individuals with cancer without diabetes, but (in relative terms) these individuals are not disadvantaged beyond that expected in the presence of diabetes and without cancer [80].

Clinical implications

For day-to-day clinical practice there are several key messages, which are grouped here as cancer screening; starting new anti-diabetes drugs; and the emergence of the *onco-diabetes* clinic.

Cancer screening

Type 2 diabetes is associated with an increased risk of some adult cancer types, independent of common risk factors such as obesity. However, these elevated risks are generally very modest. While it is important that people with diabetes partake in cancer screening programmes, in common with the rest of the general population, they do not require enhanced cancer screening. This is best illustrated by colorectal cancer screening, where some commentaries have advocated high-risk screening colonoscopy for people with diabetes [81]. For the general populations, the British Society of Gastroenterology [82] classifies risk in individuals with a family history of colorectal cancer (and without a hereditary syndrome) as moderate and subdivide this into *high-moderate* risk (lifetime risk 1 in 6–10) and *low-moderate* risk (lifetime risk 1 in 12). The recommendation in these individuals is early colonoscopy. The lifetime risk for colorectal cancer in people with diabetes is 1 in 20–40. There is therefore no need for colonoscopy screening above and beyond that in the general population.

Commencing new anti-diabetes drugs

Two hypotheses seek to explain the pathophysiological mediation between diabetes and cancer risk, namely hyperglycaemia and hyperinsulinaemia. In terms of general management of people with diabetes and the minimization of cancer risk, the extrapolation of recommendations applicable to the risk reduction of cardio-metabolic complications seems appropriate. However, there is no strong case to have cancer prevention–specific recommendations among people with diabetes. Thus, shared (cardio-metabolic) recommendations including weight management, optimal glucose management, and treatment of elevated blood pressure and dyslipidaemia are applicable.

Several anti-diabetes drug classes have been implicated in either increased (insulins, thiazolidinediones, incretin-based agents) or decreased (metformin) cancer risk. Most of the recent evidence on these questions has been reassuring. This information can be conveyed to individuals already taking these medications or about to commence these as new therapies.

The onco-diabetes clinic

Within the field of clinical diabetology, the subspecialty of onco-diabetology is emerging. It relates to the management of diabetes and related metabolic conditions in individuals with cancer and cancer survivors.

Diabetes healthcare professionals are familiar with hyperglycaemia and weight loss as symptoms of pancreatic adenocarcinoma, as well as the glucose derangements that occur with functional pancreatic neuroendocrine tumours [83], and in individuals who have undergone pancreatectomy. Similarly, the management of glucocorticoid-induced hyperglycaemia in individuals receiving chemotherapy would be considered the 'bread and butter' of most practising diabetologists [84]. Diabetes management typically worsens when an individual is diagnosed with cancer, potentially due to the psychological impact of the cancer diagnosis on the

individual, the treating physician's pessimistic perception of the person's outcome, and/or the cancer treatment [85, 86].

The survival for various cancers has vastly improved in recent years due to the rapid approval of targeted therapies. Individuals with cancer and diabetes are more likely to develop infectious [87], haematological [88], and neuropathic complications [89] from their cancer treatments, weakness from skeletal muscle catabolism [90], in addition to diabetes complications, and death from cardiovascular disease compared with those without diabetes. It is important to recognize that non-oncologists are poor prognosticators of outcomes and there are no consensus guidelines on managing diabetes in individuals with cancer. Consequently, diabetes may consequently be undertreated in this population [91]. If hyperglycaemia does contribute to worse outcomes in individuals with cancer, undertreating the diabetes may worsen cancer outcomes, although to date there are no prospective clinical trials examining how diabetes management affects responses to cancer treatment.

A second challenge for diabetes healthcare professionals is staying abreast of the advances in therapeutics in oncology, and how new cancer medications may affect glycaemic levels. Somatostatin analogues are used to treat neuroendocrine tumours and can contribute to hyperglycaemia by reducing insulin secretion. However, in some individuals somatostatin analogues can increase insulin sensitivity and reduce gastrointestinal macronutrient absorption, thereby causing low glucose levels [92].

Small-molecule pharmacological agents that target proteins in the insulin receptor or IGF-IR and related signalling pathways can also cause glucose excursions. The insulin receptor and IGF-IR are members of the tyrosine kinase family of receptors, which also includes the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR). Some of the tyrosine kinase inhibitors (e.g. EGFR inhibitors) may have off-target inhibitory effects on the insulin receptor causing hyperglycaemia, while other multikinase receptor inhibitors may cause hypoglycaemia, potentially by inhibiting insulin clearance [93, 94]. Novel inhibitors of other intermediaries in the insulin signalling pathway, such as phosphatidylinositol 3-kinase (PI3K), Akt, and mechanistic targets of rapamycin (mTOR) inhibitors, can cause severe insulin resistance and hyperglycaemia by preventing insulin-mediated glucose uptake [95, 96]. Immune checkpoint inhibitors are a class of cancer therapies that 'take the brakes off' the immune system and allow T cells to kill cancer cells. These therapies are monoclonal antibodies that target cytotoxic T-cell antigen 4 (CTLA4), programmed cell death protein 1 (PD-1), or programmed death ligand 1 (PD-L1). An uncommon but well-recognized adverse effect of these treatments, particularly the anti-PD-1 monoclonal antibodies, is destruction of the β cells of the pancreatic islets, which causes a form of type 1 diabetes [97]. Recent studies have found that these immune checkpoint inhibitors may contribute to a range of diabetes phenotypes, from insulin deficiency to severe insulin resistance with lipodystrophy, and perhaps more commonly transient hyperglycaemia [98]. Understanding the different classes of cancer treatments and the mechanisms through which these therapies contribute to glycaemic excursions is important to prevent diabetes-related complications, and in choosing the correct diabetes treatment strategy.

Finally, it is important for the onco-diabetologist to be mindful of the potential interactions between cancer therapies and diabetes medications, as well as the adverse effects of diabetes treatments that may specifically affect the oncology population. Therefore, a multidisciplinary approach involving the diabetes and oncology teams is important to improve outcomes and avoid preventable complications. The field of onco-diabetology is in its infancy and there are many aspects of this field that will likely develop over the coming years.

Conclusion

Type 2 diabetes is linked to an increased risk of several adult cancer types, though these associations are causal in probably a limited number of cancer types. Two hypotheses seek to explain the pathophysiological mediations between diabetes and cancer risk, namely hyperglycaemia and hyperinsulinaemia. Type 2 diabetes is also associated with increased cancer-related mortality, and in several countries cancer is surpassing cardiovascular disease as the commonest cause of death among diabetes populations. Several antidiabetes drug classes are additionally implicated in either increased (insulins, thiazolidinediones, incretin-based drugs) or decreased (metformin) cancer risk, and there is a large volume of laboratory evidence to support plausibility for these putative links. However, updated large-scale epidemiological analyses, using methods to reduce biases, generally weaken these associations. Compared with people without diabetes, those with diabetes who develop cancer may have a poorer response to treatment and reduced survival, but it is unclear whether this is due specifically to the adverse effects of diabetes *per se* on cancer biology or other factors like selection biases. There are three major areas of clinical implication: cancer screening in diabetes; discussing cancer risk when commencing new glucose-lowering drugs; and the management of cancer treatment-related effects in persons with diabetes, which is now leading to the emergence of the subspecialty of onco-diabetology.

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61 Diabetes and Infections

Andrea O.Y. Luk and Clive S. Cockram
The Chinese University of Hong Kong, Hong Kong SAR, China

Key points

- Diabetes is associated with an increased overall risk of infections.
- The presence of diabetes also modifies the course of many infections and increases morbidity and mortality.
- Multiple disturbances in innate immunity have a role in the pathogenesis of the increased prevalence of infections in people with diabetes. Impaired phagocytosis by neutrophils, macrophages, and monocytes; impaired neutrophil chemotaxis and bactericidal activity; and impaired innate cell-mediated immunity appear to be the most important disturbances of the immune system.
- Humoral immunity seems to be relatively unaffected, hence plasma levels of antibodies and responsiveness to most vaccinations are largely unaffected.
- Vascular disease can impair the expression of the immune response as well as affecting the overall function of the microcirculation. It is commonly a factor in severe infections such as malignant otitis externa, emphysematous pyelonephritis, and necrotizing fasciitis.
- Other factors that can predispose to infection include obesity, impaired kidney function, congestive heart failure, stroke, peripheral artery disease, and sensory neuropathy.
- Better regulation of blood glucose generally leads to an improvement in cellular immunity and function, and translates to a reduction in the incidence of severe infection.
- Some uncommon but life-threatening infections occur almost exclusively in people with diabetes. Examples include the rhinocerebral form of mucormycosis, malignant otitis externa, Fournier gangrene and emphysematous forms of cystitis, pyelonephritis, and cholecystitis.
- Increased skin and mucosal carriage of *Staphylococcus aureus* and *Candida* spp. may increase the risk of infection with these organisms. Some microorganisms become more virulent in a high-glucose environment; examples include certain *Klebsiella* serotypes and *Burkholderia pseudomallei*.
- Diabetes increases the risk of tuberculosis approximately threefold and also increases the risk of treatment failure. Unusual or extrapulmonary sites of infection may be important and cavitary disease is more common.
- Urinary tract infections and asymptomatic bacteriuria are more common in people with diabetes. Autonomic neuropathy is a common and important underlying factor.
- Skin and soft tissue infections are more common, with the infected diabetic foot as a prime example. Peripheral artery disease and diabetic neuropathy are important underlying factors in the vulnerability of the foot to infection. Skin infection or infections of the external genitalia are common presenting features of diabetes.
- Diabetes predicts a worse prognosis from coronavirus infection, including Covid-19, and people with diabetes are 2–3 times more likely to have adverse outcomes including death from Covid-19.
- Viral infections such as hepatitis C are associated with a higher prevalence of diabetes. Highly active antiretroviral therapy for human immunodeficiency virus/acquired immunodeficiency syndrome may also precipitate diabetes.

People with diabetes develop infections more often than those without diabetes and the course of the infections is also more complicated. Historically, infections have been well recognized as an important cause of death in people with diabetes and remain an important cause of morbidity and mortality. This is particularly true in low- and middle-income countries and areas, where infections are commonly the first manifestation of previously unknown diabetes. The infected diabetic foot remains a prime example of this phenomenon.

While the association between diabetes and infections is well recognized, the relationships are complex, not always clear-cut, and sometimes controversial. Data on the true incidence of certain infections are lacking and several factors complicate efforts to assess risk of infections and outcomes. Studies are often retrospective and uncontrolled in nature, with considerable between-study differences in the identification or definition of infective episodes. Furthermore, the tendency for people with diabetes to seek medical attention for minor infections and a lower threshold to initiate treatment may overestimate the number of infective episodes in diabetes populations, depending on the methods used to capture the events.

Some infections that occur predominantly in people with diabetes are uncommon and inevitably have limited data. Examples include malignant otitis externa; mucormycosis; emphysematous forms of cholecystitis, cystitis, and pyelonephritis; and Fournier gangrene. In the case of more common infections that, while not limited to people with diabetes, have diabetes as a complicating factor, many variables make for considerable heterogeneity in the clinical course. Examples include duration of disease, comorbidities such as obesity and smoking, presence of diabetes-related

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complications and other concurrent illnesses, glycaemic levels (both recent and longer term), and access to and provision of medical services.

One study, conducted in Canada, compared people with diabetes against matched individuals without diabetes for the occurrence of infection [1]. In this study, 46% of people with diabetes had at least one hospitalization or outpatient visit for infections compared with 38% of those without diabetes, with a risk ratio of 1.2. However, the risk ratios for infection-related hospitalization or death were noticeably higher, at 2.2 and 1.9, respectively. This may be attributable to increased severity and presence of complications. In the case of hospitalization, it could also reflect a lower threshold on the part of physicians to admit people with diabetes to hospital when they have intercurrent illnesses. Several other population-based studies have shown increased rates of infection in diabetes [2–5]. The rates of pneumonia were increased 1.3–1.7-fold, kidney infection 2.0–4.9-fold, skin infection 1.8–2.4-fold, osteomyelitis 4.4–15.7-fold, and general sepsis 2.1–3.2-fold in people with diabetes compared with the general population. The excess risks are in part due to the coexistence of other morbidities such as obesity, congestive heart failure, stroke, and peripheral artery disease, which are independent risk factors for infection [6]. Although the rate ratios were attenuated after adjustment for underlying medical conditions, the difference between individuals with and without diabetes remained significant, suggesting that mechanisms intrinsic to chronic hyperglycaemia and insulin resistance are also contributory.

Among studies that considered the rates in people with type 1 diabetes and type 2 diabetes separately, the risk ratios were generally higher for type 1 diabetes than type 2 diabetes [5]. In an analysis of a primary care database in the UK, the incidence rate ratio for hospitalization related to any infection was 3.7 for type 1 diabetes and 1.9 for type 2 diabetes, and death due to infection was increased 7.7-fold in type 1 diabetes and 1.9-fold for type 2 diabetes, relative to people without diabetes. Another study from Australia reporting standardized mortality ratios of deaths from infective causes revealed a 5.8-fold increase for death due to pneumonia, 29.6-fold for osteomyelitis, and 9.9-fold for sepsis in people with type 1 diabetes compared with those without diabetes [7]. The corresponding mortality ratios were 1.2, 3.3, and 1.9 for type 2 diabetes. Further evidence that the presence of diabetes can worsen the outcome of infections comes from various sources. In an early study of people hospitalized with pneumonia in Denmark, diabetes increased the risks of death at 90 days by 10% [8]. From the UK primary care database, rates of deaths related to infection were increased twofold in people with diabetes after adjustment for confounding variables [5].

An age differential for excess infection risk has been detected in several studies. In a study in Hong Kong, the disparities in rates of infection-related hospitalization between people with diabetes and the general population were greater in the young [3]. For example, hospitalization due to sepsis was 6–11-fold higher in those aged 20–44 years with diabetes compared with age-matched counterparts without diabetes, while the relative risk difference was only 2-fold for people ≥75 years.

Trend analyses on infection rates among people with diabetes have shown stagnation in incidence rates over the past 15 years. In both the USA and Hong Kong, the incidence rates of most infections including pneumonia, kidney infection, and foot infection have remained unchanged or fluctuates, while the rates of influenza have increased [2, 3]. This is concerning, because the incidence of other major diabetes complications such as cardiovascular diseases and end-stage kidney diseases have declined as a result of advances in medical care. The lack of improvements of infection rates suggests that current measures to control cardio-metabolic risk factors have not contributed to lowering infection rates.

Hyperglycaemia is an important predictor of infection and poor outcome from infection. Two independent studies of people admitted with pneumonia showed that admission glucose levels were associated with increased short-term mortality, independent of diabetes status [8, 9]. A study conducted in the UK investigated the relationships between glycated haemoglobin (HbA_{1c}) and hospitalization for infection [10]. Compared with the reference population without diabetes, people with diabetes and elevated glycaemic indices had significantly higher risks of infections than those with optimal glucose levels. In a population-based study in Mexico, death due to infectious diseases was increased fourfold in people with known diabetes and HbA_{1c} <9% (75 mmol/mol), and close to sevenfold in those with HbA_{1c} ≥9% (75 mmol/mol) [11]. People with diabetes were twice as likely to die from Covid-19 compared with counterparts without diabetes [12, 13]. During the outbreaks of severe acute respiratory syndrome (SARS) in 2003, diabetes was an independent risk factor for poor outcomes (intensive care unit admission, mechanical ventilation, and death) with a threefold increase in relative risk [14, 15]. A report from Saudi Arabia of Middle Eastern respiratory syndrome (MERS) coronavirus infection shows a 60% overall fatality rate, with underlying diabetes being present in 68% of cases, the commonest of several important comorbidities [16]. Increased severity of the clinical presentation of dengue fever has also been described, with increased representation of dengue haemorrhagic fever among people with diabetes [17]. These and other examples emphasize the importance of diabetes in both new and emerging infectious diseases and in those that are expanding their range in response to factors such as globalization and climate change.

Both host- and organism-specific factors appear to be implicated in the increased susceptibility and risk. From the host perspective, defects in innate immunity are particularly important, notably decreased functions of neutrophils, monocytes, and macrophages [18, 19]. Other factors include effects of obesity, diabetes-related complications, chronic kidney disease, poor wound healing, and frequent hospitalizations, with the attendant risk of nosocomial infection [6].

Infections may precipitate metabolic derangements, producing a bidirectional relationship between hyperglycaemic states and infection. Some infections may also be implicated more directly in the aetiology of diabetes.

Physicians working in primary care need to have high awareness of the relationships between diabetes and infection, and of the important infections that may be involved. Infections involving the foot, soft tissues, skin, and nails, as well as the urinary tract, are of particular importance as they are commonly encountered in people with diabetes, may be present at diagnosis, and may be the presenting feature that leads to the diagnosis of diabetes. Infections of the foot and skin will receive additional attention elsewhere in this textbook so, in order to avoid duplication, coverage in this chapter is curtailed. This should not be taken as an indication of lack of relative importance, the opposite being the case. The other chapters concerned should be taken as forming part of the overall coverage of the topic of diabetes and infections (Chapters 53 and 58).

Diabetes, the immune system, and host factors

Host immune response

The increased susceptibility of people with diabetes to infections is well established. Although the mechanisms remain incompletely understood, deficiencies in the host innate immune response appear to be relatively more important than changes in adaptive immunity. The innate immune system is present from birth and constitutes the first-line barrier against microorganisms. This includes physical barriers (e.g. skin, mucous membranes), phagocytes (neutrophils, macrophages, mast cells, natural killer cells), cytokines, and other inflammatory mediators. The adaptive immune system is specific to the invading microorganisms and is acquired throughout life on exposure to these pathogens. Adaptive immunity consists of T cells (cell-mediated immunity) and B cells (humoral immunity). Innate and adaptive immunity closely interact to maximize the body's defence against infection. The presence of diabetes has multiple effects on innate immune responses, including effects on neutrophils, monocytes, and other components of innate immunity, which have important roles in the increased prevalence and severity of infections. The effects include reduced chemotaxis, phagocytosis, and impaired bactericidal activity [20] (Figure 61.1).

Some disturbances in the complement system and in cytokine responses have also been described in people with diabetes (e.g. low complement factor 4 and decreased cytokine responses after stimulation), but their role in the increased susceptibility to infection is less clear [21]. Consistent defects have not been demonstrated. No clear disturbances in adaptive immunity have been described. Cell-mediated immune disturbances may be minimized by optimal glycaemic management. Humoral adaptive immunity, in particular, appears to be relatively unaffected, as exemplified by the relatively normal antibody responses to most vaccinations and the fact that serum antibody concentrations and responses are generally normal, despite the potential for glycation of antibodies such as immunoglobulin G (IgG). For example, people with diabetes respond to pneumococcal vaccine just as well as those without diabetes [22, 23].

Many studies have used *in vitro* or animal model methodology to identify the mechanisms of immune impairment and a full review of these studies is outside the scope of this chapter. However, the following observations may serve as examples from within the range of observed abnormalities.

Neutrophil chemotaxis, neutrophil adherence to vascular endothelium, phagocytosis, intracellular bactericidal activity, opsonization, and other aspects of innate immunity are all depressed in hyperglycaemic individuals with diabetes [19, 24, 25]. For instance, hyperglycaemia impairs opsono-phagocytosis by diverting nicotinic acid adenine dinucleotide phosphate (NADPH) from superoxide production into the aldose reductase-dependent polyol pathway [26]. These changes lead to reduced host defence in response to infection with extracellular bacteria. Both impaired chemotaxis and phagocytosis have also been described in monocytes of people with diabetes [27].

Defects in innate immunity predispose *db/db* mice to *Staphylococcus aureus* infections. Interestingly, however, these mice showed a heightened inflammatory response, which occurs in association with an impaired neutrophil respiratory burst, and the recruited neutrophils fail to resolve the infection [28]. Such a heightened inflammatory response may be a factor in humans with tuberculosis. In this context also, while release of tumour necrosis

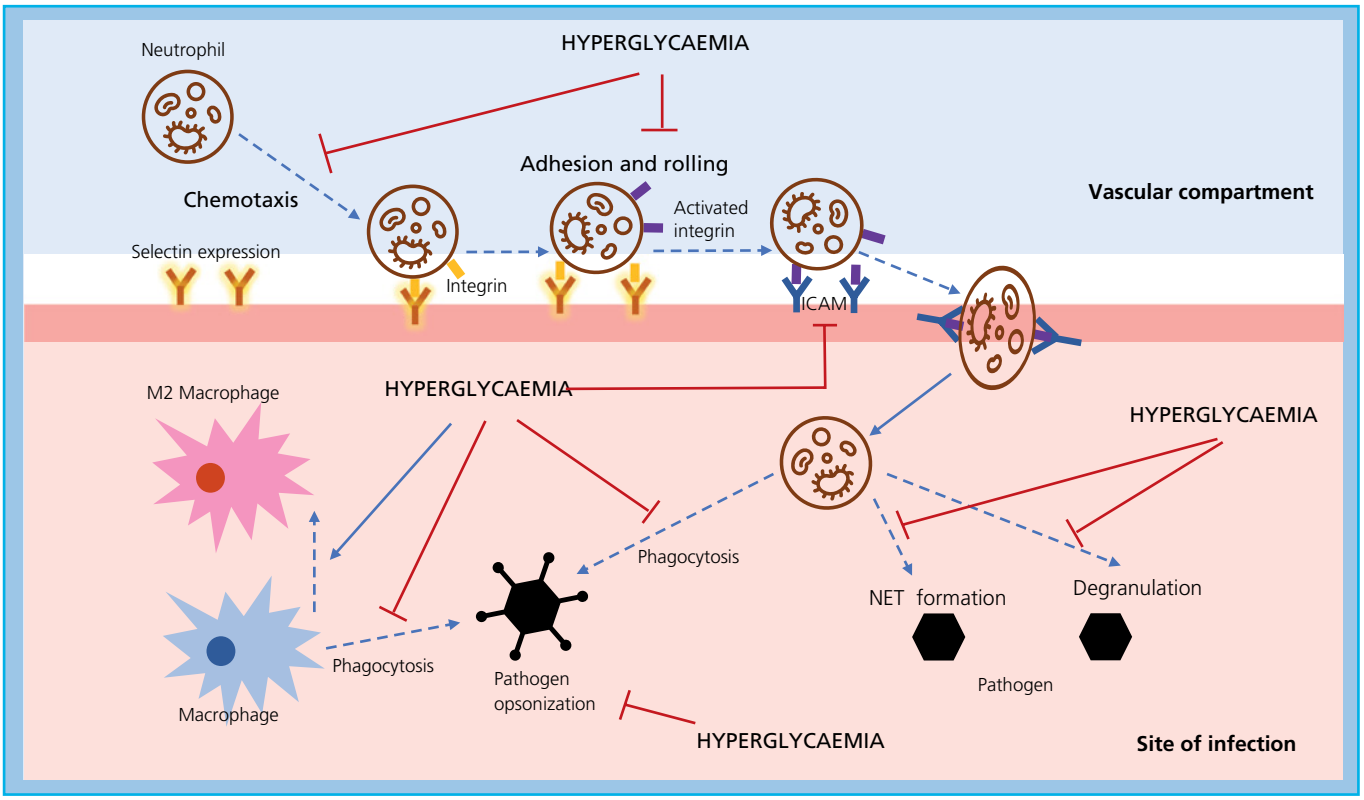


Figure 61.1 Impairment in immune response mechanisms during hyperglycaemia. Hyperglycaemia leads to impairment across a broad range of neutrophilic function, from chemotaxis, adhesion and rolling, to phagocytosis. Source: Modified by permission from Berbudi et al. 2020 [20].

factor (TNF) and interleukin 1 (IL-1) from lipopolysaccharide-stimulated macrophages is reduced in diabetic mice compared with control mice [29], study of monocytes from humans with diabetes indicates upregulation of the secretion of the same inflammatory mediators [30]. This further illustrates the difficulty of comparing studies conducted in different settings and species.

Some innate (e.g. cytokines, complement) immune functions are decreased while others remain unaffected. For example, while unstimulated cytokine concentrations may be higher, cytokine responses to stimuli are often reduced [21]. Interpretation of the complexity of the underlying mechanisms may also need to take into account potential underlying pro-inflammatory effects associated with diabetes itself. The level of macrophage inflammatory protein 2, a mediator of lung neutrophil recruitment, was significantly decreased in diabetic mice compared to control mice [31]. The deficiency causes a delay in neutrophil recruitment in the lungs. This may be one of the factors influencing the susceptibility of people with diabetes to infections of the lower respiratory tract.

Diabetic mice showed a >2-fold induction of genes that directly or indirectly induce apoptosis [32]. By contrast, blocking of apoptosis allowed for a significant improvement in wound healing and bone growth. This may influence many aspects of responses to infection, including impaired wound healing, which are important in the setting of diabetes.

These examples, while somewhat piecemeal, serve to demonstrate the range of abnormalities in the immune system that may result from hyperglycaemia. Of particular importance are those spanning macrophage, monocyte, and neutrophil function, which impair adherence to endothelium, chemotaxis, phagocytosis, and bactericidal activity. They also point to other abnormalities (e.g. involving apoptosis), wound healing, and cytokine responses to infection. The antioxidant systems involved in bactericidal activity may be compromised. These impairments, which are exacerbated by hyperglycaemia and acidaemia, may be reversed substantially, if not entirely, by normalization of pH and blood glucose levels. However, the severity of effects correlates somewhat unpredictably with direct contemporaneous measures of glycaemic levels such as HbA_{1c}, perhaps reflecting longer-term or persistent changes such as accumulation of advance glycation end-products (AGEs) [33]. A role for AGEs is postulated as a component in the pathogenesis of the impaired neutrophil function. In general, better regulation of the diabetes leads to an improvement of the cellular aspects of immune function, both innate and adaptive, despite variable correlations with HbA_{1c}.

Many questions remain as to the nature of the defects produced by diabetes, their effects on infection risk, and their exact relationship to both long- and short-term glycaemic levels, very much confounded by differences in experimental methodology.

Other host-related factors

Other host-specific factors, over and above impairment and disruption of immune defences, can further affect the predisposition to infection. These include peripheral artery disease, peripheral sensory neuropathy, autonomic neuropathy, and skin and mucosal colonization with pathogens such as *S. aureus* and *Candida* spp. Abnormalities of the structure and function of the microcirculation can also have additional indirect adverse effects on the immune responses themselves. Thus, immunological responses may be compromised by microangiopathy, and additional factors related to diabetes complications specifically increase the risks of certain infections, especially those involving the foot and the urinary tract.

Obesity, which is commonly associated with diabetes, also increases the risk of certain infections. These include nosocomial infections, wound and surgical site infections, respiratory tract infections, and infections involving the gastrointestinal tract. The presence of obesity also correlates with infected diabetic foot ulcers in people with diabetes [34].

Diabetes-related complications

Peripheral artery disease contributes to the development and progression of the diabetic foot and the attendant complications of infection, ulceration, and gangrene. Vascular insufficiency results in local tissue ischaemia that can, in turn, enhance the growth of micro-aerophilic and anaerobic organisms, while simultaneously depressing the oxygen-dependent bactericidal functions of leucocytes. The antioxidant systems involved in bactericidal activity may be compromised by the combination of microvascular disease and metabolic derangement itself. Vascular insufficiency may also further impair the local inflammatory response and the tissue penetration of antibiotics.

Neuropathy, both peripheral and autonomic, also contributes to the risk of foot infections and ulceration, as well as to certain other infections. Peripheral sensory neuropathy masks the recognition of trauma. Minor local trauma in people with peripheral neuropathy may result in skin ulcers, which, in turn, can become infected. Skin lesions are often either unnoticed or ignored until infection occurs. Autonomic neuropathy contributes to the aetiology of foot infections by mechanisms such as decreased sweating, which predisposes to drying and fissuring of the skin, and by further exacerbating abnormalities in the control of the microcirculation. Both sensory and motor neuropathy can lead to deformity and alter the dynamics of the function of the foot. Fuller discussion of the aetiological factors related to sepsis and the diabetic foot is provided in Chapter 53.

People with diabetes-associated autonomic neuropathy may develop urinary retention and stasis in association with loss of innervation to the bladder. This predisposes them to urinary tract infections (UTIs). This risk is particularly high in women. Autonomic neuropathy can also affect the function of the gastrointestinal tract, predispose to certain gastrointestinal tract infections, and contribute to the risk of aspiration pneumonia in the context of gastroparesis. Renal papillary necrosis can contribute to the risk of renal failure as well as to infection within the urinary tract. People with a history of stroke are at a heightened risk of aspiration pneumonia. Chronic kidney disease as a complication of diabetes blunts the immune system and is an independent risk factor for infection.

Organism-specific factors

Certain organisms may show increased adherence to host cells [25] and others may demonstrate increased virulence in hyperglycaemic environments. Specific factors that predispose people with diabetes to infection with specific organisms include the following examples.

Candida albicans and fungi

Glucose-inducible proteins produced by *Candida albicans* are homologous to a complement receptor on phagocytes. These proteins may promote adhesion of *C. albicans* to buccal or vaginal epithelium. This adhesion, in turn, impairs phagocytosis, giving the organism an advantage over the host [25]. Ketone reductases produced by *Rhizopus* species allow these species to thrive in the high-glucose, acidic conditions typically present in diabetic ketoacidosis [35].

***Klebsiella* spp.**

A bacterial genus of note in the context of diabetes is *Klebsiella*. *Klebsiella* infections are the second most common causes of Gram-negative sepsis (after *Escherichia coli*). In a report from Taiwan, diabetes was the most commonly associated underlying condition in people presenting with community-acquired *Klebsiella pneumoniae* bacteraemia [36]. The percentage of individuals with underlying diabetes was 49%, which was higher than in earlier reports [37, 38]. Apart from the high proportion with diabetes, associations were also observed with serotype K1 (associated with impaired phagocytosis), liver abscess, and other metastatic complications (endophthalmitis, meningitis, brain abscess) [36]. Primary liver abscess due to *K. pneumoniae* in other parts of Asia is also increasing in incidence, with 40% reportedly associated with diabetes [39].

Melioidosis

A combination of organism-specific factors together with the changes in innate immunity may explain the increased susceptibility of people with diabetes to melioidosis. About 50% of cases of melioidosis occur in people with diabetes. The responsible organism, *Burkholderia pseudomallei*, is selectively resistant to phagocytosis in the presence of diabetes.

In a study from Thailand, where melioidosis is relatively common, neutrophil responses to *B. pseudomallei*, in people both with and without diabetes, showed that *B. pseudomallei* displayed reduced phagocytosis by neutrophils compared to *Salmonella enterica typhimurium* and *E. coli*. In addition, intracellular survival of *B. pseudomallei* was detected throughout a 24-hour period, indicating intrinsic resistance of *B. pseudomallei* to killing by neutrophils. Furthermore, neutrophils from people with diabetes displayed reduced migration in response to IL-8 and an inability to delay apoptosis. Thus, *B. pseudomallei* appears to be intrinsically resistant to phagocytosis and killing by neutrophils. When added to the impaired migration and apoptosis seen in diabetes, the combination seems sufficient to explain the increased susceptibility to melioidosis [40].

Bidirectionality: the effect of infections on diabetes

Bidirectionality exists in the relationship between diabetes and infections. The effect of infections on diabetes includes the effects of certain infections on the pathogenesis of diabetes itself, effects on blood glucose levels in people with pre-existing diabetes, and exacerbation of diabetes-related complications. Infections remain an important predisposing cause of both diabetic ketoacidosis and hyperosmolar hyperglycaemia syndrome. Therefore, a careful search for underlying infection is an important part of the clinical management of acute hyperglycaemic complications.

The importance of certain viral infections in the possible aetiology of diabetes has received increasing attention in recent years with respect to both type 1 diabetes and type 2 diabetes. Viral infections have been implicated in the aetiology of type 1 diabetes for many years. Although this complicated topic is beyond the general scope of this chapter and is considered in detail in Chapters 4 and 14, it is noteworthy that the incidence of autoimmune diabetes is increasing in some regions, providing strong evidence that environmental factors are involved in the clinical expression of the disease. Viruses have long been included in the list of putative environmental triggers. Enteroviruses (especially Coxsackie B viruses), rubella, mumps, rotavirus, parvovirus, and cytomegalovirus have all been implicated and continue to be reported [41–43]. Although correlations between the presentation of diabetes and the occurrence of a preceding viral infection have been recognized, a direct causal relationship, with fulfilment of Koch postulates, remains difficult to prove, possibly because other inflammatory factors are also required. However, limited studies examining pancreatic biopsies of people with newly diagnosed type 1 diabetes have found enterovirus RNA in these specimens, strengthening the postulation that viral infection contributes to the development of type 1 diabetes [44]. In this context, the process may be associated with a dominant CD4 T-helper type 1 immune response, whereas the dominance of a T-helper type 2 response, as seen in the face of certain infectious and parasitic agents, may protect against type 1 diabetes and other autoimmune diseases. Lack of exposure to infection and infestation in early childhood appears to dilute the ability of the innate immune system to withstand autoimmune responses and challenges. Type 1 diabetes is not alone in this respect and the general concept has become known as the *hygiene hypothesis* [45]. The potential role of alterations in the gut microbiome is also receiving increasing attention and is discussed further in Chapter 19.

The high prevalence of type 2 diabetes in association with hepatitis C infection [46, 47] and the progression of certain diabetes complications, such as diabetic kidney disease, in association with hepatitis B infection are other noteworthy examples [48]. The treatment of human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) with protease inhibitors (PI) predisposes to diabetes, metabolic syndrome, and increased cardiovascular risk. Severe hyperglycaemia and higher than expected incidences of diabetic ketoacidosis among people with diabetes admitted with Covid-19 raise the possibility that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) may impair β-cell function [49–51]. The public health implications of these issues are considerable given the concordance of the diabetes epidemic with these other highly prevalent diseases.

All infections, especially if severe, have the potential to exacerbate hyperglycaemia by several mechanisms. During these periods of physical stress, the release of counter-regulatory hormones and production of cytokines such as IL-1 and TNF will worsen insulin resistance [52]. Infection remains a major factor in the pathogenesis of diabetic ketoacidosis or hyperosmolar hyperglycaemia. Infections can precipitate hypoglycaemia if symptoms, such as anorexia, nausea, and vomiting, lead to reduced food intake. Malaria and its treatment with quinine can also induce hypoglycaemia.

Hepatitis C

Reports from North America, Europe, and the Middle East consistently demonstrate an increased prevalence of diabetes (ranging from 24% to 62%) among people with chronic hepatitis C virus (HCV) infection compared both with people with other forms of liver disease and with other control groups [46, 47, 53–57]. Older age, non-white ethnicity, and the presence of metabolic abnormalities are major risk factors for type 2 diabetes in people with HCV infection [58]. The social behaviour and lifestyle of people at risk for HCV infection (e.g. intravenous drug use) could also affect the risk of diabetes. The prevalence of type 1 diabetes appears to be unaffected [58].

The suggestion that HCV infection predisposes to type 2 diabetes as a result of progressive liver damage is supported by observations that the association is most marked in older age groups

(>40 years) and that there is a higher risk among those with advanced HCV cirrhosis. The higher prevalence of diabetes in comparison with that seen in other liver diseases suggests an additional mechanism specific to hepatitis C. For instance, HCV downregulates insulin receptor substrate-1, which may contribute to insulin resistance directly. An insulin-resistant state may be further exacerbated by stimulation of proinflammatory cytokines such as TNF-α [59]. Eradication of HCV in infected individuals improves insulin sensitivity and lowers blood glucose levels [60]. In a study of people with type 2 diabetes who received direct-acting antiviral treatment for HCV infection, those who achieved a sustained virological response experienced a larger reduction in HbA_{1c} and decreased insulin requirement compared with the group who did not respond to treatment [60].

HCV infection is strongly associated with diabetes among intravenous drug users and this is independent of HIV infection or use of highly active antiretroviral therapy (HAART) [61]. Thus, it is important to monitor people with chronic HCV infection for the development of diabetes. Bidirectionality again applies with weight loss and optimal glycaemic management improving hepatitis outcomes.

HIV/AIDS

Both HIV and treatment of HIV with antiretroviral therapy predispose to type 2 diabetes, other metabolic risks, and premature cardiovascular disease [62–64]. In the Multicenter AIDS Cohort Study, men infected with HIV had a greater odds of insulin resistance than HIV-negative men, regardless of antiretroviral therapy exposure, and the incidence of diabetes was fourfold higher among HIV-infected men on antiretroviral therapy compared with uninfected men [65, 66]. In another study of over 6500 people with HIV infection, 123 developed diabetes over 28 000 person-years of follow-up, with a diabetes incidence rate of 4.4 cases per 1000 person-years [67]. An increased incidence rate ratio was found for men versus women, older age, obesity, and African American or Asian ethnicity. Strong associations were further observed with treatment using nucleoside reverse-transcriptase inhibitors (NRTI), NRTI/PI combination, and NRTI/PI/non-nucleoside reverse-transcriptase inhibitors (NNRTI) combination, but not with NRTI/NNRTI.

Diabetes and metabolic syndrome have become a major challenge in the management of this already very complicated infection [68, 69]. The effects occur via disturbances in lipid homeostasis and fat partitioning (lipodystrophy), insulin resistance, insulin secretion, and mitochondrial dysfunction. Insulin resistance is more important than impaired insulin secretion. Antiretroviral therapy for HIV-1 infection is frequently complicated by lipodystrophy (peripheral fat loss and relative visceral obesity), dyslipidaemia (high triglyceride and low high-density lipoprotein [HDL] cholesterol levels), and insulin resistance, especially with zidovudine, stavudine, and didanosine [70]. Adults infected with HIV receiving antiretroviral therapy have an increased incidence of hypertension as well as cardiovascular morbidity. Whether individuals who are naïve to antiretroviral therapy have an altered risk of subsequent cardiovascular disease or type 2 diabetes remains unclear, although insulin resistance has been reported among PI-naïve persons with HIV infection, in association with fat redistribution. People with HIV infection are more prone to hypothalamic dysfunction leading to hypogonadotropic hypogonadism and growth hormone deficiency, which predisposes to metabolic abnormalities. The key predictors of diabetes include long duration of HIV, weight gain, presence of metabolic-associated fatty liver disease, and hypertension [71].

Although the risk associated with antiretroviral therapy is greatest among individuals treated with PI attributed to a direct inhibitory effect on cellular glucose transport by PI medications, there is also an increased prevalence of diabetes among those receiving a PI-sparing regimen. Nucleoside analogue-induced mitochondrial toxicity is probably of importance. Cessation of PI appears to have little beneficial effect in reversing lipodystrophy, although it may improve the glucose levels in diabetes. Alteration of thymidine analogue nucleoside reverse transcriptase inhibitors may, however, confer benefit on lipodystrophy [72, 73]. Another study in people infected with HIV initiating antiretroviral therapy reported that higher levels of the inflammatory markers high-sensitivity C-reactive protein, soluble tumour necrosis factor receptor (sTNFR)-1, and sTNFR2 were associated with an increased risk for diabetes despite suppressive antiretroviral therapy. These data suggest that the inflammatory milieu of HIV infection may also contribute to the development of insulin resistance [74].

Lipodystrophy is a crucial aspect of the association of antiretroviral therapy with insulin resistance, leading to a relative preponderance of visceral fat, hepatic steatosis, and fat deposition at other *ectopic* sites, but loss of fat peripherally. It is of note that body mass index is not a reliable indicator of lipodystrophy. People with HIV infection and lipodystrophy, compared with those without lipodystrophy, have a reduction in plasma adiponectin and adipose tissue adiponectin mRNA levels of approximately 50%, correlating with insulin resistance and increased cytokine levels [69].

Given that baseline and incident metabolic syndrome identifies individuals at risk for both type 2 diabetes and cardiovascular disease, evaluation in all people commencing antiretroviral therapy is warranted. A fasting plasma glucose concentration should be checked before initiation of therapy and monitored every 3–6 months, especially in those receiving changes in treatment or who have significant risk factors for insulin resistance. An oral glucose tolerance test may be required, particularly in the presence of risk factors or equivocal glucose concentrations. Dietary guidelines established for the general population remain relevant for the management of glucose disorders in the context of HIV infection. Weight loss through increased activity and caloric restriction should be recommended for overweight individuals with HIV infection.

Metformin improves insulin sensitivity in people with HIV lipodystrophy and is an effective anti-diabetes medication; however, it should be used with caution in those receiving an NRTI (in particular zidovudine, didanosine, and stavudine), and in people with impaired renal function because of the possibility of lactic acidosis. The newer integrase strand transfer inhibitor dolutegravir will increase the level of metformin by decreasing renal clearance. Close monitoring is warranted and dosage adjustment of metformin may be needed. Thiazolidinediones (pioglitazone) may also improve insulin sensitivity in people with HIV lipoatrophy. Insulin therapy should be used according to standard recommendations. Substitution of an NNRTI for a PI improves insulin resistance, but this needs to be balanced against any risk to virus control. Careful discussion with HIV physicians is therefore essential and it may be deemed safer to increase the diabetes treatment rather than changing the components of the antiretroviral therapy [75–77].

Hepatitis B

Although, in contrast to HCV, hepatitis B virus (HBV) has been less consistently associated with an increased prevalence of diabetes, the presence of hepatitis B markers may nevertheless influence the

natural history of diabetes and its complications. The relationship may be bidirectional, as the presence of diabetes is associated with more severe fibrosis and cirrhosis. However, there is uncertainty as to cause and effect given the general association of diabetes with liver cirrhosis [78].

Chinese people with HBV infection and type 2 diabetes are more likely to develop end-stage kidney disease than non-HBV-infected people with type 2 diabetes (8.7% vs 6.4%), with a hazard ratio of 4.5 [48]. The association of chronic HBV infection with increased risk of end-stage kidney disease was independent of other potential confounding factors. People with HBV infection also reported earlier onset of diabetes and had a higher frequency of diabetic retinopathy than those without HBV infection (28% vs 22%). Cardiovascular complications appeared to be unaffected [48].

Specific infections either strongly associated with diabetes or in which the presence of diabetes is important

Infections involving the head and neck

Two head and neck infections that are associated with high rates of morbidity and mortality, malignant otitis externa and rhinocerebral mucormycosis, are particularly noteworthy in people with diabetes.

Malignant otitis externa

Malignant otitis externa is an invasive infection of the external auditory canal and skull base that typically arises in older people with diabetes. An early series was described in 1968 [79]. Most cases (86–90%) have been reported in people with diabetes. *Pseudomonas aeruginosa* is nearly always the causal organism (>98% of cases), although *Aspergillus* spp. or other fungi are occasionally responsible. Microangiopathy in the ear canal is a possible predisposing factor.

Presenting features include severe intractable headache and otalgia, otorrhoea, and deafness, often over a period of weeks to months. Intense cellulitis is combined with oedema of the ear canal. Focal neurological signs and cranial nerve palsies may occur. The pain may involve the temporomandibular joint and be aggravated by chewing. Osteomyelitis of the skull base and temporomandibular joint is a potentially life-threatening complication and the mortality in the pre-antibiotic era exceeded 50%. On otoscopy, granulation tissue may be seen in the floor of the ear canal, often in association with oedema and intense cellulitis. The tympanic membrane is usually intact. Computed tomography (CT) and magnetic resonance imaging (MRI) studies are essential for defining the extent of bone and soft tissue involvement, together with the bony destruction of the skull base that may be seen in advanced cases.

Systemic antipseudomonal antibiotics are the primary therapy. Early referral to an otorhinolaryngologist is essential and allows diagnostic confirmation by surgical biopsy. Debridement of necrotic tissue can also be carried out if necessary, although the introduction of effective antibiotic therapy has reduced the requirement for surgery. With the introduction of quinolones the cure rate has increased to 90%, with few adverse effects reported and oral therapy rendered possible. Prolonged treatment for 6–8 weeks is recommended, as for osteomyelitis [80]. Thus, treatment comprises prolonged administration (6–8 weeks) of an antipseudomonal agent (typically, an orally administered quinolone). The emergence of ciprofloxacin resistance is a potential problem. It is recommended that systemic quinolone use be reserved for treatment of invasive ear infections caused by susceptible pathogens. For otitis externa caused by *Aspergillus* spp., treatment would include surgical debridement and treatment with voriconazole, posaconazole, or amphotericin B. An example of invasive aspergillosis involving the skull base is shown in Figure 61.2.

Mucormycosis (zygomycosis)

The term mucormycosis is used to describe a variety of infections caused by fungi of the *Rhizopus* and *Mucor* spp. that belong to the order Mucorales (class Zygomycetes). These fungi are ubiquitous saprophytes and infections produced by them are essentially confined to immunocompromised individuals. The fungi have a predilection to invade blood vessels. Ketone reductases produced by *Rhizopus* spp. allow them to thrive in high-glucose, acidic conditions, as are typically present in diabetic ketoacidosis [35]. Rhinocerebral, pulmonary, gastrointestinal, cutaneous, and disseminated forms of the infection are described. The rhinocerebral manifestation (and with sinus involvement) has the highest frequency and is potentially the most lethal in the context of people with diabetes.

The close connection with diabetes is becoming increasingly diluted as other causes of immunocompromise become increasingly common or survivable (notably haematological cancer and bone marrow transplant recipients). Nevertheless, diabetes remains the most common underlying factor in most reports. In a review of 49 cases of pulmonary mucormycosis, diabetes was the underlying cause of the immunocompromised state in 9 (25%) [81]. In another study, the prevalence of zygomycosis and related mortality in people with diabetes was 36% and 44%, respectively [82]. It typically, although not exclusively, occurs in association with ketoacidosis, severe hyperglycaemia, and/or a debilitated state.

Rhinocerebral mucormycosis is a life-threatening fungal infection. Untreated it is universally fatal; if recognized early there is a 20% survival rate. Presenting features include facial or ocular pain and nasal stuffiness. Generalized malaise and fever may also be present. Intranasal black eschars or necrotic turbinates may be found and, if present, provide sites that can be biopsied. Treatment comprises surgical debridement of the involved sinuses and prolonged intravenous therapy with amphotericin B or alternative antifungal agents such as some newer azoles.

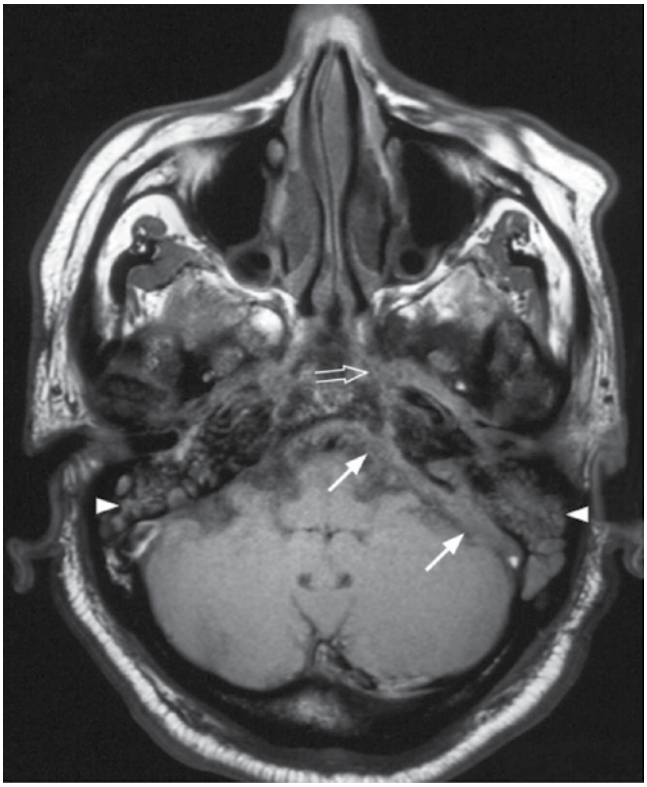
Acute invasive fungal sinusitis can also result from aspergillosis, as can malignant otitis externa. Biopsy is therefore useful to confirm the microbiological diagnosis [83].

Endophthalmitis

Secondary endophthalmitis may occur as a rare but devastating metastatic complication of septicaemia and in this setting is almost entirely confined to people with diabetes. Endophthalmitis can lead to acute vision loss and is therefore an ophthalmic emergency. Individuals typically present with progressive deterioration in visual acuity and eye pain. *E. coli* and *Klebsiella* are the more likely pathogens and UTI is reported as the most common underlying source of infection [84].

People with diabetes are also more prone to postoperative infections following eye surgery or infections secondary to eye trauma. Overall, the most common cause of endophthalmitis is as a postoperative complication of cataract surgery [85], a procedure commonly carried out in people with diabetes.

(a)



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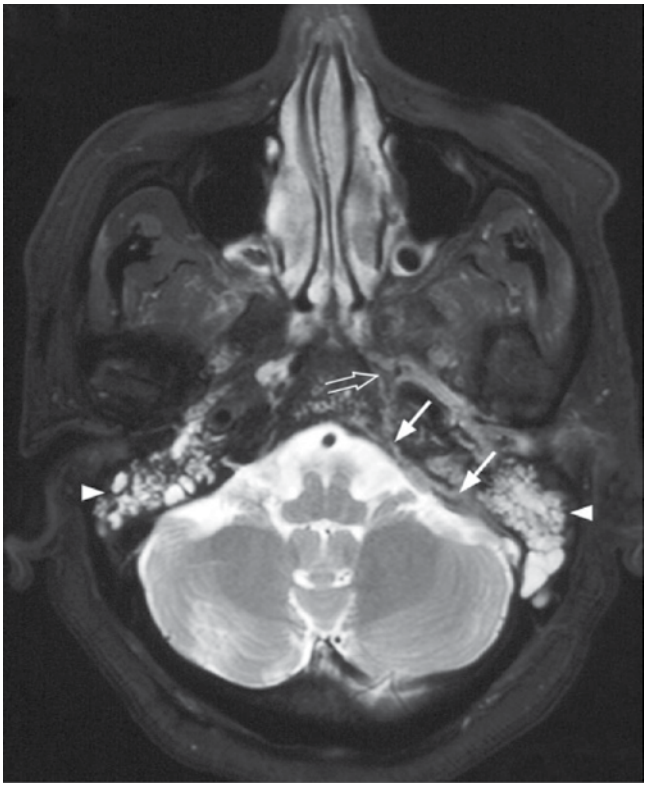


Figure 61.2 Magnetic resonance imaging (MRI) scan of skull base in a 59-year-old man with a 20-year history of diabetes (with nephropathy), treated with insulin, who developed severe extensive invasive aspergillosis. He presented with headache and vertigo followed by left sixth and seventh nerve palsies. He subsequently developed bilateral sensorineural hearing impairment and blindness secondary to extensive skull base infiltration by the invasive aspergillosis. MRI demonstrated enhancing soft tissue closely related to the left posterolateral wall of the nasopharynx with parapharyngeal, skull base, perineural, and dural infiltration. Biopsy showed inflamed fibrous tissue with degenerated fungal filaments. Culture confirmed *Aspergillus flavus*. He is receiving lifelong therapy with voriconazole. He remains blind. MRI of skull base in the axial plane with (a) T1-weighted and (b) post-gadolinium T1-weighted sequences. These show marked dural thickening (arrows) with enhancement in the left posterior cranial fossa. An abnormal signal with enhancement is also noted in the adjacent left petrous apex (open arrow). Note also the presence of inflammatory fluid within both mastoid air cells (arrowheads). Source: Courtesy of Dr K.T. Wong and Professor A. Ahuja, Department of Diagnostic Radiology and Organ Imaging, the Prince of Wales Hospital, the Chinese University of Hong Kong, Hong Kong.

Periodontal disease

People with diabetes are very prone to periodontal disease compared to the general population, with a 2–4-fold relative increase in prevalence and a particular predilection for those with elevated glucose levels.

The associated periodontitis, if left untreated, can result in loss of attachment of ligament fibres and supporting alveolar bone, which in turn can increase the mobility of teeth and necessitate extraction. Tooth abscesses and episodes of bacteraemia also become more likely. Diabetes may complicate the pathogenesis of periodontitis by causing abnormalities in the vasculature of the gingival tissues, in addition to the effects on immune responses described earlier. Aggressive and difficult-to-treat forms of periodontitis are also more common in adults with diabetes. Periodontal health is influenced by glycaemic levels to the extent that the prevalence of periodontal diseases among people with optimal glycaemia is not increased [86]. A bidirectional relationship has also been suggested whereby the presence of periodontal disease adds to the overall burden of chronic inflammation, thereby adversely affecting glycaemic levels as well as overall risk of cardiovascular disease and diabetic nephropathy [87]. Further details of periodontal disease are covered in Chapter 56.

Respiratory tract infections, coronavirus, and tuberculosis

The increased risk of mortality and morbidity from community-acquired pneumonia has been described earlier and includes pneumonia either directly resulting from, or secondary to, common infections such as influenza and *Streptococcus pneumoniae,* as well as *Legionella* infections [88]. The risk of bacteraemia following pneumococcal infection is increased [89]. Viral shedding may be more prolonged following influenza infections in people with comorbidities including diabetes, which may influence decisions regarding initiation and duration of antiviral therapy [90].

Lower respiratory tract infections, resulting from *S. aureus* and Gram-negative organisms such as *K. pneumoniae*, are more common in people with diabetes. Melioidosis has also been discussed earlier as an example of organism-specific factors that interact with diabetes to increase the risk of infection. People with diabetes are at increased risk for *S. aureus* pneumonia and this may result from higher rates of nasal carriage of *S. aureus* in people with diabetes (up to 30%) compared to healthy individuals (11%) [91]. The importance of diabetes as the most common underlying predisposing factor for thoracic empyema has also long been recognized. *Klebsiella* spp. are again notable as the most common pathogens,

while other important pathogens include streptococci, *S. aureus,* and anaerobes [92].

Respiratory infection in people with diabetes is associated with increased mortality. In the USA, people with diabetes are reportedly fourfold more likely to die from pneumonia or influenza than people without diabetes [93]. Pneumonia and influenza significantly increase the risks of acute cardiovascular events including acute myocardial infarction, and the increases in susceptibility are sustained for months after the initial infective episode [94]. Given that people with diabetes are themselves at a heightened risk of cardiovascular disease, superimposing infections are potentially detrimental.

Diabetes and coronaviruses

Covid-19 caused by SARS-CoV-2 first emerged in December 2019 and rapidly evolved into a global pandemic [95]. This medical catastrophe overwhelmed healthcare facilities worldwide. Social containment measures and travel bans caused significant disruption to daily living and the economy. Similar to severe respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV-2 is a RNA virus and originated from animals. Clinical presentation ranges from no or mild symptoms of the respiratory and gastrointestinal tracts, to acute respiratory distress syndrome, multiorgan failure, and death [96, 97].

Diabetes was previously reported to be an important predictor of severe disease and death in people infected with SARS-CoV and MERS-CoV [14–16]. Observational studies from China, the USA, and other countries indicated that diabetes was associated with adverse outcome and mortality from Covid-19 [12, 13], although it remains unknown whether diabetes increases the opportunity of acquiring the viral infection, as high-quality data related to the diabetes status of people with Covid-19 managed in the community are not available. Among cohorts of people hospitalized with Covid-19, the prevalence of diabetes ranged between 7% and 24%, which overlapped with diabetes prevalence among the general population [95, 98]. However, diabetes was present in between 13% and 58% of people who required admission to intensive care units, and between 17% and 35% of people who succumbed had pre-existing diabetes [99–102]. Overall diabetes was associated with a 2–3-fold hazard of mortality related to Covid-19 [12, 13].

Several mechanisms may explain the worse prognosis from Covid-19 in people with diabetes. People with diabetes have a dysregulated inflammatory response to infection with SARS-CoV-2. Compared with infected counterparts without diabetes, those with diabetes had higher levels of pro-inflammatory biomarkers, including C-reactive protein, IL-2 receptor, IL-6, IL-8, TNF-α, and procalcitonin [103, 104]. The exaggerated inflammatory response facilitates the development of cytokine storm, severe pulmonary damage, and multiorgan failure. Furthermore, endothelial dysfunction and prothrombotic state in diabetes might contribute to disseminated intravascular coagulation, which may be the terminal event in Covid-19. The coexistence of obesity in people with diabetes further exacerbates severe progression [105]. Obesity predisposes to altered ventilatory mechanics and function, such as reduced lung compliance and apnoea.

The overexpression of angiotensin-converting enzyme 2 (ACE2) in people with diabetes has been implicated in their propensity for Covid-19 and SARS [106]. ACE2 is an aminopeptidase expressed in the respiratory tract and other organs. ACE2 on the alveolar cells is the primary receptor for both SARS-CoV and SARS-CoV-2, and increased ACE2 expression may potentiate viral entry [107]. However, ACE2 counters the pro-inflammatory and vasoconstrictive action of angiotensin II by converting angiotensin II into angiotensin [1–7], the latter having an antioxidant function. The use of renin–angiotensin–aldosterone system (RAAS) inhibitors, which augment ACE2 levels, lowers the risk of pneumonia in people with or without diabetes [108]. In the context of Covid-19, available research indicates a neutral effects of RAAS inhibitors on mortality or critical outcome [109–111].

ACE2 is also present on pancreatic β cells and it is possible that these viral infections can induce diabetes by direct damage to the pancreatic endocrine tissues. Based on clinical reports, insulin requirement in people with Covid-19 was disproportionately high to the level of physiological stress when compared with other critical infections or acute medical illnesses [49–51]. Several groups also reported a high frequency of diabetic ketoacidosis among hospitalized people with Covid-19, suggesting virus-induced acute insulinopaenia and metabolic decompensation [49]. Other explanations for the severe hyperglycaemia include lapses in glucose-lowering medications during city lockdown and quarantines, and the use of high-dose corticosteroid as part of Covid-19 management. Some but not all studies found increased incidence of diabetes post-Covid-19. In a study conducted in the USA, people who previously had Covid-19 had a 1.5-fold higher risk of receiving a diagnosis of diabetes over a one-year observation, and the excess risks were similar across age groups, BMI, and diabetes risk scores [112]. In another population-based study conducted in Germany, exposure to SARS-CoV-2 was associated with a 28% increased risk of type 2 diabetes compared to exposure to non-Covid-19 respiratory tract infections [113]. In contrast, longitudinal follow-up of people discharged after Covid-19 in England did not find an increase in diabetes incidence versus admission for non-Covid-19 pneumonia [114]. Whether or not Covid-19 can induce diabetes remains unclear and further work is needed to understand the virus's long-term metabolic impact.

Data are conflicting regarding the effect of glycaemic levels on the risk of coronavirus infection and outcome. There was a positive association between HbA_{1c} before hospitalization and mortality from Covid-19 in some but not all studies [13, 115]. However, high blood glucose on admission was most consistently predictive of severe disease, irrespective of diabetes status. A small study comparing insulin infusion versus no insulin infusion in people with in-hospital hyperglycaemia showed that insulin treatment reduced inflammatory and coagulation indices and improved outcome [116]. Limited evidence also indicated that in-hospital use of dipeptidyl peptidase 4 inhibitors lowers fatality [117].

Diabetes and tuberculosis

An association between diabetes and tuberculosis has been widely accepted in the past, and solid epidemiological evidence has emerged in the last decade to establish firmly a close link. Systemic reviews have confirmed that people with diabetes are approximately threefold more likely to develop active tuberculosis than people without diabetes, albeit with varying estimates of overall risk (ranging from 2- to 11-fold) [118, 119].

The importance of the association is often neglected in the larger arena of public health, for example when compared with the risk of tuberculosis associated with HIV. The increase in risk appears consistent across geographical regions, regardless of both study design and background incidence of tuberculosis. It appears greatest among younger people in areas of high tuberculosis incidence and

in non–North American populations [118]. The public health impact may be particularly high in low- or middle-income countries or areas that are at the forefront of the diabetes epidemic and where tuberculosis remains endemic [119–121], and may therefore be particularly high in countries such as China and India. In Hong Kong, the risk differential for tuberculosis between people with and without diabetes has remained unchanged over a 10-year period [3]. Moreover, the excess risk for tuberculosis was two- to threefold for middle-aged people with diabetes, but climbed to sevenfold for those aged 20 and 44 years.

The impact of the diabetes epidemic on tuberculosis incidence in India has been previously modelled [122]. Diabetes accounted for 15% of pulmonary tuberculosis and 20% of smear-positive tuberculosis, with an excess risk of the latter in urban areas. This can be compared to an overall estimate of 3.4% for the proportion of adult tuberculosis incidence ascribed to HIV/AIDS in India [123]. Given the vast number of people living with diabetes, the impact of diabetes on tuberculosis incidence will be immense at a population level.

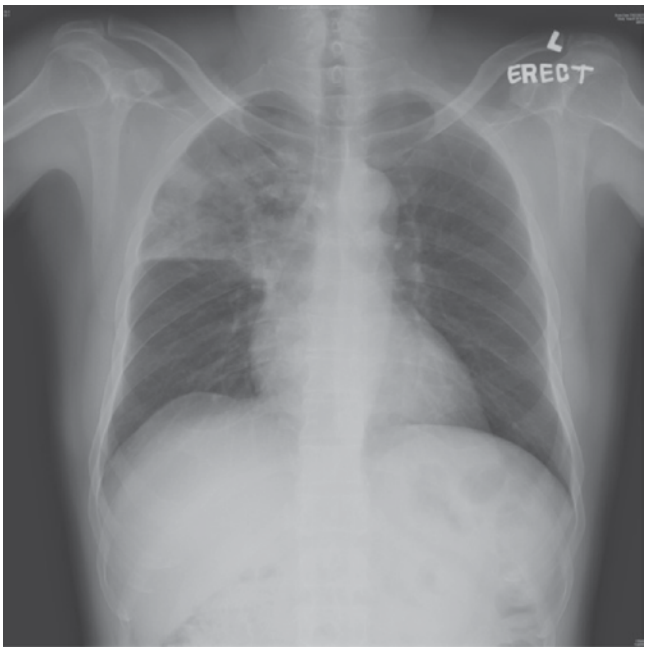
The association of tuberculosis with diabetes reflects impaired innate immunity as well as a reduced adaptive T-helper type 1 response, with reduced secretion of T-helper type 1–related cytokines, thereby increasing the risk of progression from tuberculosis infection to active disease as well as increasing the risk of latent tuberculosis following initial primary infection. Regarding the clinical presentation, extrapulmonary or unusual manifestations of tuberculosis are more common in the context of diabetes. People with tuberculosis and diabetes are more likely to develop opacities over the lower lung fields, extensive parenchymal lesions, any cavity, multiple cavities, and large cavities compared to those without diabetes, and these radiological abnormalities are more common in the presence of suboptimal glycaemic levels [124, 125].

In addition to the increased risk of tuberculosis, people with diabetes are at increased risk of worse outcomes, including treatment failure, relapse, and mortality [126]. People with diabetes are more likely to remain smear positive after 2–3 months of treatment, as shown in six of nine studies evaluating sputum conversion [126]. A study from Indonesia indicated a doubling of the risk of remaining smear positive at the end of treatment [127]. The same group has also shown that the presence of type 2 diabetes may adversely affect the bioavailability of rifampicin and lead to an increase in dose requirement [128]. A study from Brazil found that those with tuberculosis and diabetes had poorer treatment outcomes even after adjusting for confounding factors [129].

One of the options to improve treatment outcomes might be to extend the period of treatment. In Hong Kong, an area with much pioneering experience of tuberculosis treatment since the 1950s, the Centre for Health Protection recognizes the risk of a worse outcome, and its guidelines recommend a more prolonged period of treatment for people with diabetes compared to those without. For example, when treating pulmonary tuberculosis using a standard regimen of four drugs for the first two months followed by two drugs, a total treatment duration of nine months, rather than six months, is recommended. Two examples of individuals with tuberculosis in association with diabetes are shown in Figure 61.3. It is perhaps noteworthy that neither was receiving regular follow-up care for the diabetes.

Bidirectionality again needs to be considered, because the presence of tuberculosis is likely to worsen hyperglycaemia. Tuberculosis, as

(a)



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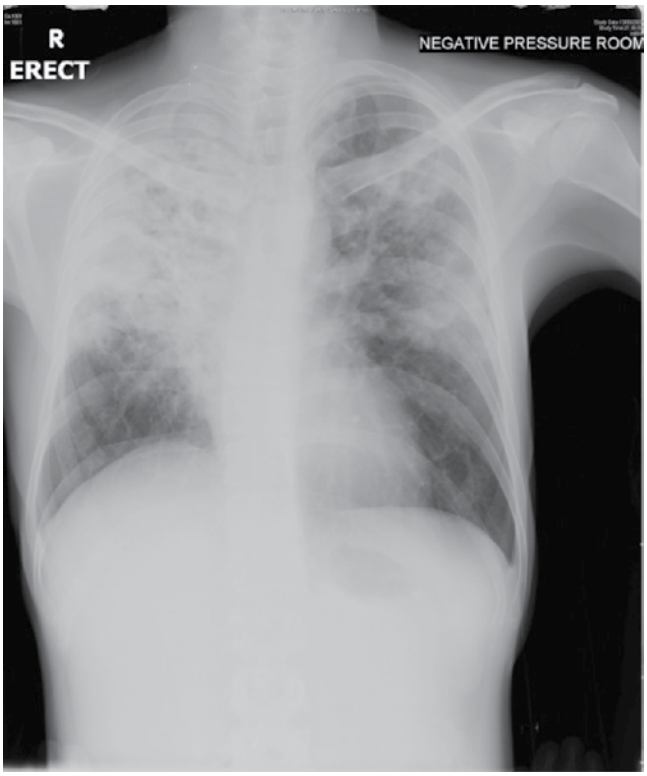


Figure 61.3 (a) A 49-year-old man with diabetes and obesity, not receiving regular follow-up, and presenting with haemoptysis and sputum smear positive for tuberculosis. Chest X-ray shows extensive right upper lobe pneumonic changes. (b) A 30-year-old man with diabetes but no regular follow-up presenting with a cough for four months with weight loss, and sputum smear positive for tuberculosis. Chest X-ray shows extensive bilateral and cavitatory disease.

with other infectious diseases, can lead to deterioration of glycaemic levels and complicate the management of diabetes. Unpredictable effects on glycaemic levels may result from alterations in inflammatory processes, changes in appetite and body weight, and, importantly, drug–drug interactions. In this connection, acute deterioration of glycaemic levels without other obvious explanations should prompt investigation for occult infections such as tuberculosis, especially in areas of high prevalence. Rifampicin, the most important drug, increases the hepatic metabolism of sulfonylurea drugs, although with large inter-individual variation. It may also lead to an enhanced glucose-lowering effect of metformin [130]. Some national treatment guidelines (e.g. in Indonesia) strongly recommend the use of insulin therapy, since insulin has no direct pharmacokinetic interactions with rifampicin or other anti-tuberculous agents. Thus, people with concurrent diabetes and tuberculosis may have specific needs during treatment, including close monitoring of glycaemic levels and renal and hepatic function, as well as counselling and education. There is a strong case to be made for integrated care linked with service and policy development [130]. The issue of screening is pertinent, both for diabetes in people with tuberculosis and for tuberculosis in people with diabetes.

Diabetes and influenza

Influenza is responsible for half a million deaths globally every year, and older people and those with chronic diseases are at particularly high risk of death from influenza. In an earlier study conducted in the working population in the USA, prevalent diabetes increased the odds of death from influenza or pneumonia fourfold [93]. In a large multinational study of people hospitalized with influenza, the odds of severe disease, defined as the requirement for mechanical ventilation, admission to the intensive care unit, or in-hospital death, increased 3.9-fold in those with concurrent diabetes aged 15–50 years, although no disparity was detected between older individuals with and without diabetes [131]. In addition to causing respiratory distress, influenza also increases the risk of acute coronary events. The reasons are multifactorial, related to systemic inflammation causing activation of inflammatory cells in atherosclerotic plaques, a prothrombotic state triggering coronary thrombosis, and increased metabolic demand causing cardiac decompensation.

Annual vaccination against seasonal influenza is recommended for people with diabetes. There were concerns on whether seroprotection may be suboptimal in people with diabetes, but available studies showed no differences in immune responses to influenza vaccination between people with and without diabetes [132]. Studies on vaccine effectiveness were mostly observational in nature, with inherent limitation of residual confounding. For instance, people who received vaccination were more likely to engage in health-seeking behaviours, which could biased towards favourable health outcomes. Nonetheless, several studies have reported protection against influenza- and pneumonia-related hospitalization and all-cause hospitalization [133]. Using population-level data from a Danish diabetes registry, people who have received vaccination for seasonal influenza had a 17% lower risk of all-cause death and a 16% lower risk of cardiovascular death, adjusted for sociodemographics and comorbidities [134]. Despite these benefits, vaccine coverage varies considerably across countries. Generally, high-income countries with established guidelines and influenza vaccination programmes have higher coverage than middle- or low-income countries. Ongoing efforts are required to increase awareness among healthcare professionals and the public to reduce the burden of vaccine-preventable diseases.

Infections of the urinary tract

Epidemiology

Urinary tract infections are frequently encountered in people with diabetes. Asymptomatic bacteriuria also occurs with a higher frequency [135]. One study has demonstrated a prevalence rate for asymptomatic bacteriuria of 26% in women with diabetes, compared to 6% in women without diabetes [136, 137]. An increased prevalence of asymptomatic vaginal *E. coli* colonization has also been reported in postmenopausal women receiving insulin treatment. This colonization may be mediated by greater adherence of type 1 fimbriated *E. coli* to uroepithelial cells in women with diabetes, may be related to impaired cytokine secretion, or may reflect a reduced polymorphonuclear inflammatory response [136, 138]. A randomized controlled trial of antibiotic treatment for asymptomatic bacteriuria revealed no differences in the development of symptomatic UTI, time to onset of symptoms, risk of pyelonephritis, or need for hospitalization [136]. On this basis, diabetes does not warrant either screening for or treating asymptomatic bacteriuria. However, this remains a controversial issue and, from the practical standpoint, ascertaining *asymptomatic status* with confidence, particularly in older women with diabetes, can be difficult.

Studies confirm the increased risk of symptomatic UTI in association with diabetes. In one study of more than 600 women, those with type 2 diabetes had an overall risk of 20% [139]. A recent study has extended the risk to include recurrence rates as well as risk to men [140]. Diabetes also increases the risk of complications of UTI, serious or unusual forms of infection, and need for prolonged hospitalization [141]. It is a risk factor for acute pyelonephritis in women and is the strongest of the various risk factors examined. Among hospitalized individuals, 16.7% reported having diabetes compared with 5.8% of non-hospitalized people [136].

Diabetic autonomic neuropathy is an important predisposing factor to UTI. This affects the sympathetic and parasympathetic afferent fibres to the bladder and causes decreased reflex detrusor activity. Impaired bladder sensation results in bladder distension, increased residual urine volume, vesicoureteric reflux, and recurrent upper UTI [142, 143]. Some cases are related to urinary catheterization or instrumentation [136, 142, 143]. Additional factors predisposing to UTI include glycosuria, sexual intercourse, a history of previous UTI, obstruction, longer duration of diabetes, hyperglycaemia, decreased urinary cytokine excretion, increased *E. coli* adhesion, macroalbuminuria, and neutrophil dysfunction [142, 143]. Renal papillary necrosis and chronic renal failure also contribute to the complex array of risk to the urinary tract. Lastly, the use of sodium–glucose cotransporter 2 (SGLT-2) inhibitors is associated with increased risk of genital tract infections but not urinary tract infections [144].

Microbiology

E. coli is the most commonly reported organism. *Klebsiella* is also a problem, especially among individuals with uncommon severe forms of UTI, such as emphysematous pyelonephritis. Other organisms include *Acinetobacter* spp., group B streptococci, and *P. aeruginosa* [135]. The latter should be suspected particularly if there is a history of recent instrumentation or hospitalization.

C. albicans in the urine can be associated with incomplete bladder emptying and high glucose concentrations in the urine. Diabetes is present in 39% of hospitalized individuals with funguria [135]. Candiduria may signify contamination of the urine specimen, benign saprophytic colonization (±catheter), or be indicative of true invasive infection of the upper and/or lower urinary tract [145].

Diabetes is a risk factor for multidrug-resistant UTI, perhaps related to recurrent or increased exposure to antibiotics [146].

Clinical features of urinary tract infection in diabetes

Uncomplicated UTIs may be asymptomatic. Symptoms, when present, are generally similar to those experienced by people without diabetes. Infection of the lower urinary tract usually presents as dysuria, frequency, or urgency. Fever, flank pain, chills and rigours, vomiting, and costovertebral angle tenderness raise the suspicion of upper tract infection with renal involvement. Bilateral renal involvement is also more frequent and bilateral pyelonephritis is twice as common in people with diabetes. Bacteraemia may be present.

A poor response to appropriate antibiotic therapy should raise the suspicion of the presence of complications. These may include renal papillary necrosis and perinephric abscess. The symptoms of renal papillary necrosis include flank and abdominal pain (which mimic both pyelonephritis and ureteric colic), together with fever. Renal impairment is commonly found. Features such as a persisting high fever despite antibiotic treatment, hypotension or septicaemia shock, and a palpable tender renal mass may point to the presence of a perinephric abscess. In one series of people with perinephric abscess, 36% had diabetes [147].

Emphysematous cystitis and emphysematous pyelonephritis

Although these infections are uncommon, their severity warrants their special consideration. Emphysematous cystitis is an uncommon complication of lower UTI characterized by the presence of gas in the bladder wall (Figure 61.4). It presents with haematuria, pneumaturia, and abdominal pain. Plain abdominal radiography or CT scan is indicated to detect the presence of gas. Surgical intervention may be required in up to 20% of cases and mortality is reportedly up to 10%. Emphysematous cystitis requires aggressive treatment in hospital and intravenous antibiotic therapy [149].

Emphysematous pyelonephritis is an infection that is almost exclusively limited to people with diabetes, who account for 90% of cases (Figure 61.5). It predominantly occurs in women and carries a grave prognosis [151]. It is a necrotizing infection of the renal parenchyma and surrounding areas that can be focal or diffuse and may spread to the collecting system or perinephric tissues. The formation and presence of gas in the renal parenchyma, collecting system, or perinephric area may be contributed to by fermentation of glucose, when present at high concentrations, by the presence of gas-forming organisms, and by impaired renal perfusion. Mixed acid fermentation of glucose by *Enterobacteriaceae* has been suggested as a major pathway of gas formation [152].

A lengthy list of pathogens has been reported; however, as with other UTIs in the context of diabetes, the most common pathogens are *E. coli* (in 70%) and *Klebsiella* (in 30%). Vasculopathy of the renal circulation is a major factor in the pathogenesis, once again emphasizing the importance of vascular disease in the clinical manifestation of the more severe forms of infection related to diabetes. Presenting features include fever, abdominal pain, nausea and vomiting, and drowsiness or stupor. As a result of these non-specific symptoms, the diagnosis is often delayed. The presence of features such as renal angle tenderness, pyuria, or pneumaturia should lead to a high index of suspicion. A flank mass may be detected, often accompanied by crepitus. Disseminated intravascular coagulation, septicaemic shock, and acute renal failure are all associated with a poor prognosis.

The diagnosis is established by radiological identification of gas in renal tissue. Ultrasonography can also be used, but CT should be regarded as the investigation of choice. The plain abdominal X-ray sensitivity is lower. In a report of 46 cases in Taiwan, 96% had diabetes with HbA_{1c} higher than 8% (64 mmol/mol), and 22% also had features of obstruction [153]. Mortality can exceed 50% in people treated only with antibiotics. Medical therapy alone is therefore not recommended. People with diabetes may require percutaneous drainage (for localized cases with abscess formation or obstruction) or nephrectomy (in extensive cases). The advent of CT has allowed a more rational approach to the use of these surgical interventions, by allowing more accurate delineation of factors such as gas distribution, obstruction, and abscess formation [154].

Figure 61.4 Example of emphysematous cystitis in a 67-year-old woman with diabetes and end-stage kidney disease requiring haemodialysis. She developed septic shock with lower abdominal tenderness. Blood and urine cultures showed *Escherichia coli*. Computed tomography scan shows air pockets inside the urinary bladder (arrows). Source: Sun et al. 2009 [148]. Reproduced by permission of Oxford University Press.

Treatment of urinary tract infection

Treatment should be tailored to take account of local antibiotic resistance patterns (if known), as well as previous history of UTI, previous antibiotic exposure (and possible allergies), together with other risk factors such as recent instrumentation or catheterization. Uncomplicated UTI may be treated with co-trimoxazole (if the local resistance rate is <15% to 20%), fluoroquinolones, nitrofurantoin, ampicillin, amoxicillin ± clavulanate, or sulbactam. Increasing

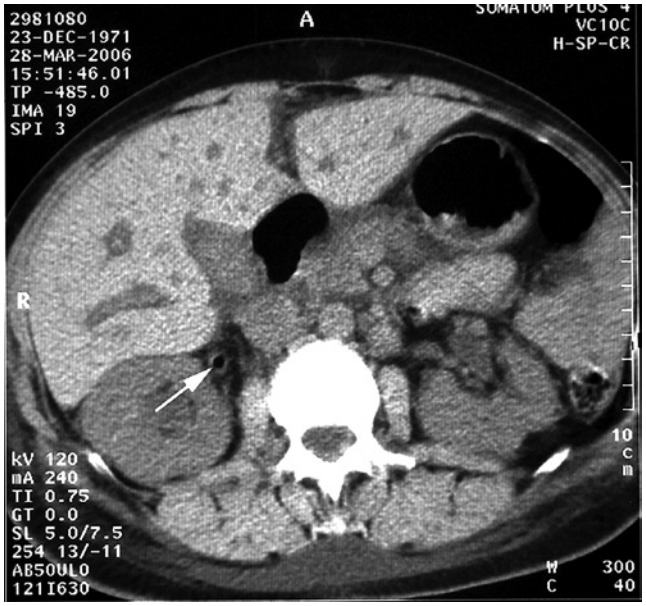


Figure 61.5 Emphysematous pyelonephritis: computed tomography scan demonstrating gas in the right ureter (arrow) and moderate hydronephrosis in a 34-year-old woman with type 1 diabetes. The responsible organism was *Escherichia coli*. She responded to antibiotics and drainage by nephrostomy, followed by ureteroscopy during which obstructing necrotic slough was removed. Source: Reproduced by permission from Clark et al. (2009) [150]. Copyright © 2009 SAGE Publications.

resistance to fluoroquinolones has been noted recently. Co-trimoxazole may potentiate the hypoglycaemic effect of some anti-diabetes drugs and should be used with caution.

Complicated infections require hospitalization and parenteral antibiotics. Intravenous therapy is continued until fever resolves, following which oral antibiotics can be substituted to complete at least two weeks of treatment. Second- or third-generation cephalosporins, β-lactam/β-lactamase inhibitor combinations, or fluoroquinolones may need to be considered in individuals with risk factors. The possibility of infection with *Pseudomonas* may influence this choice, particularly in the setting of nosocomial exposure or recent instrumentation.

Upper urinary tract involvement with UTI may be up to fivefold more frequent in people with diabetes compared with people without diabetes and may be unsuspected or asymptomatic. More prolonged courses of antibiotics (7–14 days) may be considered wise even in the context of apparently uncomplicated UTI. This may also reduce the risk of subsequent relapse. Repeated urine culture to document bacteriological cure 2–4 weeks post-treatment is advisable given high rates of relapse or treatment failure.

Distinguishing *Candida* infection from colonization is difficult. Removal of an indwelling catheter, if present, is recommended as an initial intervention. Antifungal agents such as fluconazole may be considered in people with invasive disease.

Intra-abdominal infections other than those within the urinary tract

The potential for interaction between diabetes and various infections of the gastrointestinal tract is considerable and a few examples are considered here. In this context, although the presence of increased risk of *Helicobacter pylori* infection in people with diabetes remains controversial, the presence of diabetes may, in turn, reduce the effectiveness of antibiotic regimens aimed at eradicating the infection. The presence of gastritis may also influence the endocrine functions of the gut, as well as the absorption and handling of oral anti-diabetes drugs such as metformin.

Emphysematous cholecystitis

Cholecystitis is probably no more common in people with diabetes than in the general population. However, severe fulminating infection, especially with gas-forming organisms (enteric Gram-negative rods and anaerobes), is more common. An association between gallbladder stones and the use of glucagon-like peptide-1 receptor agonists has been reported [155]. Given the increasing use of this drug class in people with diabetes, a rising trend in the incidence of cholecystitis or other gallstone-related diseases may be anticipated.

Emphysematous cholecystitis is a rare variant of acute cholecystitis caused by ischaemia of the gallbladder wall and infection with gas-producing organisms. It is strongly associated with diabetes (35–55% of cases have underlying diabetes) [156]. Gangrene and perforation of the gallbladder are more frequent, and the overall mortality is substantially higher (at least 15% compared to less than 4%) in individuals with emphysematous cholecystitis when compared with those with acute cholecystitis. *Clostridium perfringens*, *E. coli*, and *Bacillus fragilis* are the most frequently encountered pathogens. Emphysematous cholecystitis results from acalculous cystic duct obstruction, associated with inflammatory oedema, which can eventually lead to cystic artery occlusion. Colonization by gas-forming organisms contributes to necrosis of the mucosa, venous congestion, gangrene, and eventually gallbladder perforation. Gallstones are present in only about half of the individuals.

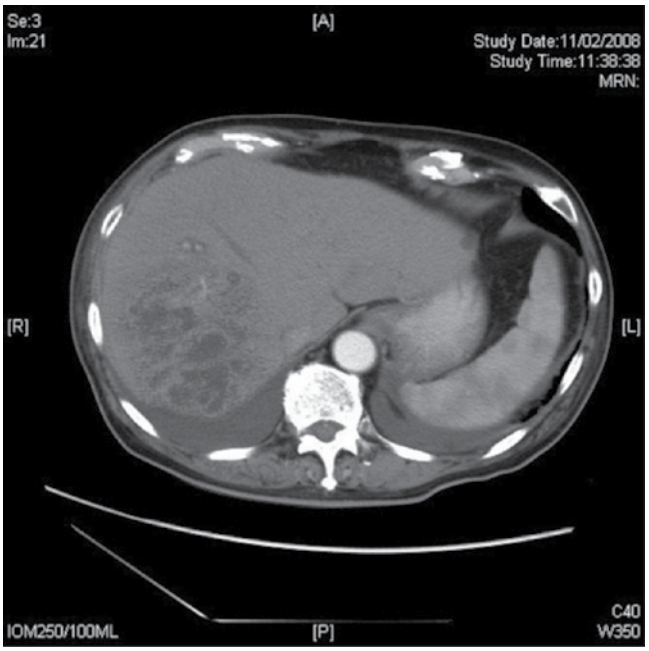
The early clinical manifestations may be indistinguishable from those of acute cholecystitis. Right hypochondrial pain and fever are present in all cases, and other important features include nausea and vomiting, septic shock, jaundice, and peritonitis. Toxicity is marked, and jaundice may develop in the later stages from biliary obstruction. The gallbladder may be palpable in 25–50% of individuals. It should be remembered that Murphy's sign (pain and inspiratory arrest on palpation of the right upper quadrant) might be absent in people with underlying diabetic neuropathy. Crepitus on palpation is an ominous sign. Additional complications include pericholecystic abscess, gallbladder necrosis, generalized or biliary peritonitis, and localized perforation sealed by the omentum.

Plain abdominal X-ray or ultrasound can lead to diagnosis in 95% of cases. In a plain radiograph, gas may be visible in the gallbladder lumen or within the gallbladder wall as a gaseous ring. Abdominal CT is the most sensitive modality for the detection of intraluminal or intramural gallbladder gas and also demonstrates local complications such as pericholecystic inflammatory changes, abscess formation, or perforation. Initiation of appropriate antibiotics and early cholecystectomy are crucial. Emergency surgery is needed because of the high incidence of gangrene and perforation [157, 158].

Liver and other intra-abdominal abscesses

Although liver abscesses may occur in many situations not involving diabetes, the issue is of sufficient importance to justify inclusion in this section. In keeping with the susceptibility to *Klebsiella* infections described earlier, associations between diabetes and *K. pneumoniae* liver abscess have been reported, notably from Taiwan and Korea [159–161]. In Korea, invasive liver abscess is particularly associated both with *K. pneumoniae* (78% of the total, 40% of whom have diabetes) and with the K1 serotype (60%) [39]. Examples from Hong Kong are shown in Figure 61.6.

(a)



(b)

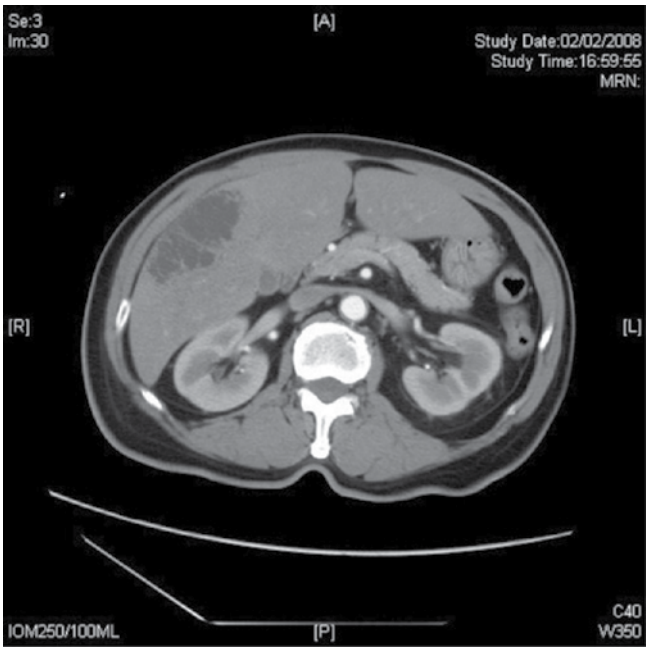


Figure 61.6 (a) Computed tomography (CT) scan of an 82-year-old man with fever and newly diagnosed diabetes. Blood culture grew *K. pneumoniae*. The scan shows an 8 × 8.2 cm heterogeneous lesion in the right lobe of the liver composed of multiple rim-enhancing lesions, with septation and hypodense cystic components. A further three smaller similar lesions (1–2.5 cm) were seen inferiorly. Overall features are suggestive of liver abscesses. He recovered with drainage and antibiotics. (b) CT scan of a 77-year-old woman with underlying diabetes, fever, and right upper quadrant pain. Both blood culture and pus (from the liver abscess) grew *K. pneumoniae*. The CT scan shows an irregular ovoid lesion with multiple locules and thin intervening septations in the periphery of liver segment V and measuring 7.3 × 3.2 × 6.1 cm. The features suggest liver abscess with signs of early liquefaction. The woman recovered with drainage and antibiotics. Source: Courtesy of Department of Diagnostic Radiology and Organ Imaging, the Prince of Wales Hospital, the Chinese University of Hong Kong.

Diabetes is the most common underlying risk factor specifically for the virulent K1 serotype, but not for non-*Klebsiella* abscesses [162]. In a population-based series of pyogenic liver abscess reported from Taiwan and including 29 703 participants [163], diabetes was a risk factor in 33%, leading to a relative risk of 9.1. Liver abscess in people with diabetes was not, however, associated with increased mortality, particularly if therapeutic percutaneous drainage procedures were performed. In 80% there was an association with *K. pneumoniae* and not as a mixed infection with other organisms. Primary liver abscess in other parts of Asia is also increasing in incidence [39], with 40% reportedly associated with diabetes. Bacteraemia is present in 50%, and 8–10% of these cases have metastatic complications (e.g. endophthalmitis, meningitis, brain abscess, pneumonia, or skin and soft tissue lesions).

In a series from Europe (n = 1448), the presence of diabetes was associated with a 3.6-fold increase in risk for pyogenic liver abscess, and also with a higher 30-day post-discharge mortality rate compared with people who did not have diabetes [164]. In the context of the K1 serotype of *Klebsiella* species, a pathogenic role for the *magA* gene in the serotype-specific region of the K1 capsule gene cluster, together with a K1 capsular polysaccharide *per se*, is considered as one of the virulence determinants essential for the development of invasive liver abscess. MagA, an outer membrane protein contributing to capsular polysaccharide formation, coexists with serotype K1 and is the major virulence factor of *K. pneumoniae* [163]. Suboptimal glycaemic levels also have a role by impairing neutrophil phagocytosis of K1/K2-type *K. pneumoniae*, whereas it does not significantly affect the phagocytosis of non-K1/K2 *K. pneumoniae*. A regulator of mucoid phenotype A–associated hypermucoviscosity phenotype has also been reported in invasive purulent diseases caused by *K. pneumoniae*.

Most isolates are susceptible to cephalosporins (especially third-generation agents) and fluoroquinolones; however, therapeutic drainage is also needed and assists with obtaining specimens for culture and susceptibility testing. Metastatic abscesses may occur elsewhere in the abdomen, either singly or in combination with other sites, as well as within the urinary tract. A notorious, although uncommon, example is psoas abscess, where responsible organisms are likely to be *S. aureus*, *Mycobacterium tuberculosis*, *E. coli*, or *Klebsiella*.

Skin and superficial soft tissue infections

Skin and subcutaneous tissues

Infections involving the skin, nails, and subcutaneous tissues are very common, and the skin and subcutaneous tissues are frequent targets of infection in diabetes, particularly in association with suboptimal glycaemic levels. Candidal infections, bacterial infections such as furunculosis, dermatophycoses, and onychophycoses are all commonly seen and may be the reason for diabetes being identified. Cutaneous forms of mucormycosis or other fungal infections may occur and be diagnosed following skin biopsy. More detailed consideration is given to these disorders in Chapter 58.

Sensory neuropathy, atherosclerotic vascular disease, and hyperglycaemia predispose people with diabetes to skin and soft tissue infections. Additional risk factors for the development of cellulitis include a past history of cellulitis, oedema, peripheral vascular disease, tinea infection, and dryness of the skin. The predominant

organisms involved are group A streptococcus and *S. aureus*. Cellulitis can also occur in less usual settings. For example, with *S. pneumoniae* (pneumococcal) infections, cellulitis may occur in association with extracutaneous foci of disease, the suggestion being that, in this setting, the cellulitis results from haematogenous spread rather than local infection [165].

People with diabetes, particularly those who inject insulin, often have asymptomatic nasal, mucosal, and skin colonization with potential pathogens such as *S. aureus*. Nasal colonization may contribute to an increased risk of staphylococcal pneumonia, for example in association with influenza. According to data from the US National Health and Nutrition Examination Survey, people with diabetes who were colonized with *S. aureus* were also more likely to have a methicillin-resistant *S. aureus* isolate than a susceptible one (odds ratio 2.6) [166]. A previous increase in community-associated methicillin-resistant *S. aureus* (CA-MRSA) gives additional cause for concern. A report evaluating CA-MRSA in three communities found that 77% of skin or soft tissue infections were methicillin resistant [167]. The underlying conditions identified included smoking (35%), previous skin infection (21%), and diabetes (19%). As people with diabetes are more frequently hospitalized or attend healthcare facilities, they are at increased risk of being exposed to more virulent strains of these bacteria and hence more likely to be colonized.

Mucosal and skin colonization with *C. albicans* are also common and may involve numerous sites, including the genitalia of both sexes as well as the mouth, skin, and nails [168]. Balanitis and vulval candidiasis are common presenting features of diabetes. Colonization may predispose to cutaneous or incisional staphylococcal (or other bacterial) infections as well as transient bacteraemia. Entry sites may also include areas of fungal skin infection (e.g. intertrigo). Infection at distant sites with abscess formation or septicaemia may then ensue. In two relatively early studies (each from the 1960s), older people with diabetes were shown both to be at greater risk of staphylococcal septicaemia and also to suffer a substantially higher mortality (69% in those with diabetes vs 42% overall) [169, 170].

Deeper soft tissue infections

Deeper soft tissue infections also occur with increased frequency in people with diabetes. Examples include pyomyositis, necrotizing fasciitis, and Fournier gangrene. Pyomyositis, usually associated with infection by *S. aureus*, occurs in muscles that have undergone trauma, especially when associated with haematoma formation. Of note is that skin abscesses are a common initial presentation of type 2 diabetes in susceptible individuals.

Necrotizing fasciitis

Necrotizing fasciitis is a deep-seated life-threatening infection of subcutaneous tissue. Progressive destruction of fascia, fat, and muscle ensues. Although relatively uncommon, necrotizing fasciitis is a life-threatening condition. Necrotizing fasciitis and Fournier gangrene (a form of necrotizing fasciitis involving the perineum), as well as other necrotizing soft tissue infections resulting from a variety of organisms, all have reported associations with diabetes. Diabetes is the most common of several conditions predisposing to necrotizing fasciitis, all of which are associated with compromise to the immune system.

As its name indicates, necrotizing fasciitis spreads initially along fascial planes. As infection and inflammation progress, necrosis of muscle, subcutaneous tissues, and overlying skin occurs. Necrotizing fasciitis usually follows identifiable episodes of trauma such as burns, insect bites, or abrasions, or can result from exposure of non-intact skin to a source of infection. The most common sites are the limbs, abdominal wall, and perineum. Involvement of the vulva in women with diabetes may begin as a Bartholin gland ductal abscess, usually associated with obesity [171].

Polymicrobial infection is most commonly observed, with streptococci and *Enterobacteriaceae* being the most common isolates. The great majority of cases result from infection with anaerobes together with one or more facultative aerobes, whereas about 10% are associated with group A streptococcus, with or without *S. aureus*. Thus, group A streptococcus is the most common cause of infection by a single organism and can also occur in combination with staphylococci, including CA-MRSA. A recent article describing necrotizing fasciitis caused by CA-MRSA showed that although current or past intravenous drug abuse underlay 43% of cases, 21% occurred in people with diabetes [172]. *Vibrio*, *Aeromonas*, *Haemophilus*, and *Salmonella* infections have also been reported. An interesting example is infection by halophilic marine *Vibrios*, either following exposure of non-intact skin to seawater [173] or following bites by marine organisms, such as crabs, and this should be considered when a history of appropriate exposure is present.

Necrotizing fasciitis carries a high mortality, particularly when affecting the lower extremities or perineum, and is rapidly fatal unless diagnosed promptly and treated aggressively. It may be initially misdiagnosed as a benign soft tissue infection and a high index of suspicion is therefore required. Skin changes may be minimal in the early phase of infection.

Early disease may be characterized by severe local pain, which is either disproportionate to or precedes other clinical features such as local inflammation and cellulitis, fever, and systemic toxicity. Cellulitis may spread rapidly, unseen in deeper fascial planes. Crepitus is present in about half of cases. Violaceous discoloration of the skin may be noticed and may progress into blistering and bullae. Thrombosis and vasculitis both contribute to necrosis of the superficial fascia and suppuration from liquefactive necrosis. Gangrene and ulceration can result. Anaesthesia of overlying skin may indicate destruction of subcutaneous nerves.

Plain radiographs, ultrasound, CT, and MRI scan can assist in both diagnosis and management by identifying the presence of gas in the tissues and by delineating the extent of the disease. Aerobic and anaerobic cultures should be taken from within the lesion, as should blood cultures.

Surgical debridement and fasciotomy are the mainstays of therapy. The single most important issue influencing mortality is time to surgical debridement. Thus, timely diagnosis, empirical broad-spectrum antibiotic therapy (including anaerobic cover), and aggressive surgical debridement of affected tissue are crucial components of management. The antibiotic cover can subsequently be tailored according to culture and sensitivity results. Additional supportive therapy in an intensive care environment should be provided where possible and as necessary.

Fournier gangrene

Fournier gangrene is a specific form of necrotizing fasciitis involving the perineum, scrotum, and penis. Overall mortality is very high. As with other forms of necrotizing fasciitis, diabetes is the most common of potential predisposing conditions, with a reported presence ranging between 32% and 60% of cases [174, 175]. Infection is usually polymicrobial, with a lengthy list of potential pathogens that is similar to that seen in other forms of necrotizing

fasciitis (*E. coli*, *Bacteroides* spp., staphylococci, streptococci, *Proteus* spp., *Pseudomonas* spp., enterococci). *C. perfringens* is present in the great majority (>90%) of cases in which myonecrosis is present.

Initial malaise and scrotal discomfort or pain is followed by systemic toxicity. Blistering ulceration and necrosis of the skin occur and in the later stages progress to scrotal swelling and a foul purulent discharge. Crepitus may be present. Sources of infection include abnormalities of the urogenital system (most notably urethral trauma, instrumentation or a chronic indwelling catheter, scrotal abscess or injury, insect bite) and local gastrointestinal abnormalities (e.g. ischiorectal or perianal abscess, incarcerated inguinal hernia).

Diagnosis is predominantly clinical. Imaging techniques may reveal subcutaneous gas and delineate the extent of involvement, as with other forms of necrotizing fasciitis.

Fournier gangrene is a surgical emergency, and extensive debridement is required. Urinary or faecal diversion may be required, as may laparotomy. Broad-spectrum antibiotic therapies with anaerobic cover, as well as general supportive measures, are indicated as with other forms of necrotizing fasciitis. The results of microbiological investigation may allow subsequent tailoring of antibiotics.

Infected diabetic foot

Foot infection is the most common soft tissue infection associated with diabetes and therefore is a topic of the utmost importance to all who deal with people with diabetes. A specific chapter (Chapter 53) is devoted entirely to this topic. Thus, in order to avoid duplication, the subject receives only brief discussion in this chapter.

Foot infection occurs as a complication of diabetic foot ulcer, for which peripheral neuropathy and peripheral artery disease are both important factors, although the clinical presentations of the *predominantly ischaemic* and the *predominantly neuropathic* foot differ. Serious complications include osteomyelitis, amputation, or even death. Infection often begins after minor trauma, which may be unnoticed, especially in the presence of sensory neuropathy. Cellulitis, soft tissue necrosis, and extension into bone, leading to osteomyelitis, may then follow. Involved organisms most commonly include group A streptococcus and *S. aureus*, as well as aerobic Gram-positive cocci, Gram-negative rods, and anaerobes.

The mainstays of management include exploration and debridement of the necrotic tissue and administration of appropriate antibiotics. In moderate to severe cellulitis or in the presence of osteomyelitis that places the limb at risk, the person should be hospitalized for broad-spectrum antibiotic therapy and surgical intervention.

As in most diabetes-related infections, suboptimal glycaemic management plays an important part, and foot infections remain a common presenting feature of newly diagnosed diabetes, particularly in low- and middle-income countries. Prevention of foot ulcers involves a multidisciplinary team approach. Foot care is an essential component of all diabetes education programmes and should include proper foot care habits, protective footwear, and pressure reduction.

Bone and joint infections

Bone and joint infections remain a significant problem for people with diabetes and can be very difficult to treat. Diabetes is a risk factor for both osteomyelitis and septic arthritis. The different types of osteomyelitis require differing medical and surgical therapeutic strategies. The three main types, classified according to aetiology, include osteomyelitis secondary to a contiguous focus of infection (e.g. after trauma, surgery, or insertion of a joint prosthesis); osteomyelitis secondary to vascular insufficiency (e.g. diabetic foot infections); or osteomyelitis secondary to hematogenous spread of infection. The most common reason for septic arthritis is following insertion of joint prostheses. All are more common in people with diabetes, with osteomyelitis of the foot at the forefront. Taking as an example osteomyelitis of the spine, a recurring theme occurs with a combination of both increased risk of haematogenous vertebral osteomyelitis (2–6-fold) and predisposition to infection involving unusual organisms [176]. Acute osteomyelitis can respond to antibiotics alone, but prolonged courses are required for bone and joint infections given the physiological and anatomical characteristics of the tissues involved. Early imaging using MRI or CT, together with bone sampling for microbiological and pathological examination to allow targeted and long-lasting antimicrobial therapy, provides the best outcomes. As with the diabetic foot, a multidisciplinary approach is required for success, including expertise in orthopaedic surgery and infectious diseases, together with vascular surgery. Surgical intervention should be considered if medical treatment fails, for diagnostic confirmation, or in the presence of complications.

Chronic osteomyelitis may be associated with avascular necrosis of bone and formation of sequestrum (dead bone), and surgical debridement is then necessary for cure in addition to antibiotic therapy. It is important to remember the possibility of infection by *M. tuberculosis* [177].

Iatrogenic and surgical site infections

Insulin injections

Infections at the site of insulin injections are very uncommon and remain so even when traditional hygienic practices are not applied. Although not advised, administration of insulin through clothing is also not associated with increased risk of infection. Abscesses at needle sites are occasionally seen in individuals receiving subcutaneous insulin infusions [178]. Likewise, pulp infection over the distal phalanges in association with self-blood glucose monitoring is exceedingly unusual.

Surgical site infections

An association between diabetes and an increased risk of surgical site infections has been recognized for many years. The association has been generally assumed to be causally related to the deleterious effect of hyperglycaemia on immune function [179]. Some studies showed a reduced risk of infectious complications such as pneumonia and wound infection in people with satisfactory preoperative glycaemic levels compared with those with less optimal levels [180]. Other studies found glucose levels in the postoperative period to be more strongly related to infection risks than preoperative glycaemic measures [181–183]. In a retrospective study of 995 people with or without pre-existing diabetes undergoing general or vascular surgery, the risk of infection was increased 30% with every 40 mg/dl (2.2 mmol/l) increase in postoperative glucose level from normoglycemia (110 mg/dl [6.1 mmol/l]) [184]. In a clinical trial evaluating continuous intravenous insulin infusion versus intermittent subcutaneous insulin injection, the former resulted in lower postoperative glucose levels and reduced incidence of deep wound infection [185].

Both allograft rejection and risk for infection appear to be higher in transplant recipients with diabetes. In one study, the risk of serious infection was higher in heart transplant recipients with diabetes in the early postoperative period [186]. In another study,

kidney transplant recipients had a greater risk of both acute allograft rejection and infection when perioperative glycaemic levels were elevated [187].

Dialysis

Ambulatory peritoneal dialysis is a common form of treatment for end-stage kidney disease in people with diabetes, especially in Asia. For those receiving continuous ambulatory peritoneal dialysis, episodes of catheter-related peritonitis are common, although variable from individual to individual, with some developing multiple episodes. Overall, however, the rate of infection does not appear to be greater in people with diabetes than those without diabetes, perhaps reflecting the impairment of immunity associated with end-stage kidney disease *per se*.

The issue of peritonitis in people receiving continuous ambulatory peritoneal dialysis is an important one given the large number of those with diabetes receiving this treatment. It is well recognized that peritonitis, despite significant reductions in the last two decades, remains the most important complication of continuous ambulatory peritoneal dialysis with an overall mortality of about 3.5%, irrespective of both the underlying cause of the infection and the renal failure [188]. The degree to which the presence of diabetes adds to the already considerable infection risk remains uncertain. People with diabetes may, however, be generally more unwell and have additional factors and complications such as cardiovascular disease, need for hospitalization, and predilection to certain infections, such as candidiasis. All of these may, in principle, contribute to the already very considerable risk.

Principles of treatment, prevention, and general care

General principles

A high level of awareness is required in people with diabetes and in all healthcare providers, both to allow prevention and to enable early, prompt recognition and diagnosis. Education, good glycaemic management, and general steps to maintain health and nutrition are all important measures aimed at minimizing risk. Careful attention to foot care is particularly emphasized. Vigilant measures should be instituted to prevent infection. This includes personal hygiene and avoidance of crowds, especially during peak influenza seasons. When infections do occur, evolving antibiotic resistance patterns and other local factors must be considered, with CA-MRSA and tuberculosis both providing obvious examples of the importance of this.

The choice of antibiotic therapy follows the same general principles as for any other individual. Use of empirical broad-spectrum antibiotics is generally recommended until microbiological results can guide treatment. Due caution should be applied in the presence of diabetes-related complications. For example, the use of potentially nephrotoxic agents in the context of diabetic kidney disease may aggravate kidney impairment and, in turn, people with kidney disease require caution with doses and monitoring of blood levels. The presence of gastroparesis or autonomic neuropathy may hinder, or render unreliable, the absorption of oral drugs. People who are blind or partially sighted as a result of eye complications may also be at increased risk, for example when exposed to drugs that impair hearing or balance. Longer courses of antibiotic therapy may be appropriate, for instance in treating UTI.

Antiviral agents are recommended in the setting of influenza, and a more aggressive treatment approach may be appropriate even when presentation is relatively late [90]. Responses to treatment should also be carefully monitored (e.g. in the case of tuberculosis) [127]. The importance of appropriate referral to surgical or other specialist colleagues has been stressed repeatedly. Examples include surgical debridement in the case of necrotizing fasciitis, and incision and drainage of abscesses.

People with diabetes generally have a normal response to vaccines and should receive immunizations according to established guidelines. None of the vaccines currently available is contraindicated on the basis of diabetes alone. Because of increased susceptibility to complications, routine immunization against pneumococcus and influenza is recommended, particularly for older people with diabetes and for those with additional comorbidity such as chronic respiratory disease. Influenza vaccination reduces influenza- and pneumonia-related hospital admissions as well as all-cause death during influenza outbreaks [133, 134]. Hepatitis B vaccination is also important, although some populations may require additional or booster doses over and above standard recommended regimens.

Glycaemic management

All physicians need to be aware of the importance of careful monitoring of glycaemia in the presence of infection and should be on guard against destabilization of glycaemic levels or development of complications. Interestingly, in people without diabetes following hospitalization, even mild degrees of hyperglycaemia are associated with increased mortality in association with severe illness. Although depressed immune function correlates somewhat variably with traditional glycaemic measures, there is sufficient evidence to indicate an inverse relationship between the two that is potentially reversible. Previously undiagnosed diabetes may also be first detected following hospitalization and then needs to be distinguished from hospital-related hyperglycaemia that later reverts to normal.

People with type 1 diabetes or others receiving insulin need to be aware of the probability of changing insulin requirements in response to infection and to the risk of severe consequences such as diabetic ketoacidosis. Many people with type 2 diabetes who are not using insulin need to be transferred temporarily to insulin therapy as the stress of illness frequently adversely affects glycaemic levels. Hospital admission is mandatory if severe destabilization of glycaemia occurs, or if symptoms such as nausea and vomiting interfere significantly with oral food intake. In this situation, intravenous insulin–glucose regimens are recommended. People using SGLT-2 inhibitors should be informed to temporarily withhold this medication during sepsis. While optimal glycaemic levels are important, it is also important to avoid hypoglycaemia. Interaction between the diabetes care team and other involved specialists should be initiated as early as possible.

The importance of perioperative glycaemic management in people with diabetes undergoing surgery needs to be emphasized in order to minimize negative impacts on postoperative infection rates and wound healing (Chapter 58). Attention to other risk factors (e.g. neurological and vascular complications) is also important to minimize the risk of infections and infection-related complications. The importance of the presence of vascular disease and neuropathy in the risk of the more severe forms of infection is again stressed. For more detailed description of these aspects of care, readers are referred to clinical practice recommendations, for example those of the American Diabetes Association, or to other national or international guidelines, as well as to other relevant chapters in this textbook.

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62 Sleep and Diabetes

Sonya Deschênes[1], Amy McInerney[1], and Norbert Schmitz[2,3,4]

[1] School of Psychology, University College Dublin, Dublin, Ireland
[2] Department of Psychiatry, McGill University, Montreal, Canada
[3] Douglas Mental Health University Institute, Montreal, Canada
[4] Department of Population-Based Medicine, University of Tübingen, Tübingen, Germany

Key points

- Sleep quality and duration are associated with diabetes progression and management.
- The association between sleep and diabetes is complex and incorporates behavioural, environmental, physiological, and psychological factors.
- Sleep apnoea, restless leg syndrome, insomnia, and long and short sleep duration are common sleep problems associated with diabetes.
- Renal dysfunction, neuropathy, and retinopathy are common complications in diabetes that are associated with sleep disorders.
- Depression frequently co-occurs with both sleep disorders and type 2 diabetes and may also function as a mediator between poor sleep and diabetes self-management difficulties.
- People with diabetes may benefit from the screening of sleep impairments as they are common comorbidities, influence well-being, and complicate diabetes management.
- Large longitudinal observational studies, using objective sleep measurements, are needed to further shed light on the role of sleep in the development and progression of diabetes and its complications.

Sleep, a behavioural process that is influenced by circadian, neurohormonal, and homeostatic processes [1, 2], is critical for optimal functioning and well-being. The important role of sleep can be highlighted by the consequences when it is deficient. Sleep deficiency is linked with adverse effects on behaviour and cognition [3], increased risk of road traffic incidents [4], impaired immune function, increased pain, impaired performance, increased errors [5], and increased risk of disease [5–7]. The fast-paced, 24/7 nature of modern society, with increasing use of technology and on-demand entertainment in the home, may be compromising the population's ability to obtain adequate sleep. Some evidence suggests that these lifestyle and social changes have happened concurrently with an increase in complaints of sleep problems and symptoms of sleep disorders [8, 9]. However, other research suggests mixed findings regarding the changes in global patterns of sleep duration [10], particularly in studies with adults [11]. Nevertheless, suboptimal sleep and sleep disorders are now considered as modifiable factors having adverse impacts on global health [12, 13].

The relationship between sleep and health outcomes appears to be reciprocal and complex. Sleep problems and disorders co-occur frequently in chronic health conditions [14, 15], and can also serve as potential pathways to chronic disease through their effects on bodily systems such as the endocrine, metabolic, and immune systems [16, 17]. Among those with diabetes, sleep disorders and atypical sleep duration have been associated with diabetes complications [18], while complications of diabetes can, in turn, impair sleep [19, 20]. This chapter will discuss common sleep problems and disorders, their relationship with diabetes and diabetes complications, and their associations with diabetes management.

Sleep problems

Sleep problems are often used as a general term for having trouble falling asleep, difficulty maintaining sleep, or the subjective experience that sleep has not been sufficiently refreshing or restorative. Sleep problems can leave a person feeling exhausted and take a serious toll on their health and well-being. Worldwide, studies have reported the prevalence of sleep problems in the general population as ranging from 1.6% to 56% [21, 22]. Sleep problems are typically assessed using self-report questionnaires such as the Pittsburgh Sleep Quality Index [23]. Polysomnography is considered the gold standard for the assessment of sleep problems [24]. However, it is often impractical to assess sleep habits and patterns over multiple consecutive days in non-clinical settings. Actigraphy-based sleep measures have been suggested as alternative measures for the identification of sleep problems [25].

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Sleep disorders

Sleep disorders are conditions that affect an individual's ability to obtain quality sleep on a regular basis and, when chronic, can have long-term effects on health. The most recent edition of the International Classification of Sleep Disorders lists 83 sleep disorders [26]. The International Classification of Diseases 11th Revision (ICD-11) codes categorize sleep–wake disorders into insomnia disorders (i.e. difficulty in falling and staying asleep), sleep-related breathing disorders, sleep-related movement disorders, hypersomnolence disorders (i.e. excessive sleepiness), circadian rhythm sleep–wake disorders (i.e. disorders of the sleeping schedule), and parasomnia disorders (i.e. abnormal physiological or behavioural events that happen while sleeping) [27].

Insomnia

Insomnia is the commonest sleep disorder in the adult population [28]. Insomnia involves both nocturnal and diurnal symptoms and is characterized by a dissatisfaction with quality and/or quantity of sleep, difficulty falling asleep, frequent or early-morning awakenings, mood disturbances, daytime fatigue, and impaired attention and concentration [26, 29]. Worldwide, the proportion of the general population self-reporting that they experience symptoms of insomnia is approximately 30% [30]. However, the percentage meeting the criteria for a diagnosis of insomnia has been estimated between 5.8% and 15.8% [31, 32].

Sleep apnoea

Sleep apnoea, a relatively common sleep disorder, is characterized by the absence of inspiratory airflow for at least 10 seconds during sleep [33]. The two main types of sleep apnoea are obstructive sleep apnoea (OSA) and central sleep apnoea (CSA). OSA syndrome involves recurrent episodes of partial or complete upper-airway obstruction during sleep [27]. These obstructions often cause reductions in blood oxygen saturation and end with a brief awakening from sleep [27]. CSA is characterized by reduced or ceased airflow due to a lack of respiratory effort [27] from a reduction or cessation in the central neural outflow to the muscles of the respiratory system during sleep [34]. In a review of population-based studies, the prevalence of OSA was reported as approximately 22% (range 9–37%) in men and 17% (range 4–50%) in women [35]. While there is less research on the prevalence of CSA, it has been estimated as less than 1% in the general population [36], and is higher in chronic opioid users [37] and those with heart failure [38].

Restless leg syndrome

Also known as Willis-Ekbom disease, restless leg syndrome is diagnosed based on five diagnostic criteria:

- An urge to move legs due to discomfort when resting.
- The urge usually being accompanied by pain or paraesthesia.
- Temporary relief of symptoms with movement.
- A circadian aspect, wherein the symptoms worsen during the evening or night.
- The symptoms not being the result of another medical condition [39, 40].

A recent 2018 aggregate of studies found a mean prevalence of 4.6% (range 2–9.4%) in men and 8.6% (range 2.3–15.4%) in women [41]. The strong urge to move the legs at night makes it difficult to fall and stay asleep, leading to sleep deprivation and, thus, significant distress and diminished quality of life [27, 42].

Sleep duration (long and short sleep)

Sleep duration is often defined as the total amount of time spent asleep over a 24-hour period [43]. Optimal sleep duration varies between individuals. Recent guidelines from the US National Sleep Foundation recommend 7–9 hours of sleep for young and middle-aged adults and 7–8 hours of sleep for older adults [44]. However, the prevalence of short sleep duration is common. In 2017 in the USA, an estimated 32.9% of people slept less than 6 hours, 59.8% slept between 7 and 8 hours, and 7.3% slept over 9 hours [45]. While there are regular reports in the popular and academic literature that we are sleeping less now than in the past, recent reviews indicate more inconsistent findings: sleep duration is declining in some countries but increasing in others, with no certain social or economic explanations for international differences [11].

Sleep timing and consistency

Sleep timing refers to the time of day when sleep occurs (i.e., bedtime and wake-up time), while sleep consistency refers to the intra-individual variability in sleep timing and sleep duration, with high consistency characterized by an individual's regularity in sleep timing and duration [46]. Alternative shift work and rotating night work are becoming increasingly common in industrialized countries [47], which can lead to sleep inconsistency. Shift work can lead to circadian dysregulation or disruption of circadian rhythms (normal sleep–wake cycle) due to inconsistent sleep times. As circadian alignment of sleep is an important factor for metabolic health [48], individuals with inconsistent sleep are at risk for experiencing adverse metabolic consequences [49]. A recent meta-analysis [50] reported that atypical sleep duration was associated with various poor health outcomes [51–53]. It concluded that regularity in sleep patterns, with a consistent wake-up and sleep time, should be encouraged for maintaining good health. However, the review also stated that existing studies have focused on linear associations. Quantifying what is considered acceptable sleep variability and healthy sleep timing remains unclear. It was recommended that future research focus on exploring the dose–response relationship between sleep and health outcomes, such as mortality, quality of life, work productivity, and other chronic diseases [50].

Sleep problems or disorders and diabetes

The association between sleep disorders and diabetes is multifaceted and bidirectional (Figure 62.1). Diabetes can lead to sleep disturbances through polyuria, nocturia, and painful neuropathy [54]. Some of the most common sleep disorders and problems among those with diabetes are sleep apnoea, insomnia, restless leg syndrome, and short and long sleep duration [55]. Emerging research has demonstrated associations between diabetes complications and sleep disorders [18]. Renal dysfunction, neuropathy, and retinopathy

are common diabetes complications associated with sleep disorders [55]. Most research has focused on sleep problems in people with type 2 diabetes, but several studies support the role and influence of sleep on poor outcomes in people with type 1 diabetes, although evidence from high-quality clinical and observational studies is lacking [56]. A summary of the evidence on sleep problems in people with type 1 diabetes is presented first, followed by a discussion of the associations between sleep and type 2 diabetes.

Sleep duration and type 1 diabetes

Of the few existing studies examining the prevalence of short and long sleep duration in type 1 diabetes, one found that 16% of adults with type 1 diabetes obtained less than six hours of sleep per night [57], although another study found no significant differences in sleep duration between adults with type 1 diabetes and matched participants without diabetes [58]. In addition, longer sleep duration has been associated with decreased insulin sensitivity [59]. Shorter sleep duration is associated with greater glycaemic variability [60] and higher glycated haemoglobin (HbA_{1c}) levels [61]. A meta-analysis revealed a relationship between self-reported sleep duration and glycaemia, with average HbA_{1c} levels 0.24% (3 mmol/mol) higher among those sleeping less than six hours [62].

Sleep quality and type 1 diabetes

A study by van Dijk and colleagues [58] suggested that 35% of adults with type 1 diabetes self-reported poor sleep quality compared with 20% of those without diabetes. However, no significant association was found between individual sleep quality and HbA_{1c}. Similarly, Denic-Roberts [57] found that 41% of adults with type 1 diabetes reported poor sleep quality (51% in women, 30% in men) and Martyn-Nemeth et al. found poor sleep quality in 46% of adults with type 1 diabetes [63]. Poor sleep quality also seems to be associated with decreased insulin sensitivity [59].

Obstructive sleep apnoea and type 1 diabetes

A high prevalence of OSA has been reported in adults with type 1 diabetes. For instance, of 200 individuals with type 1 diabetes attending an outpatient clinic, OSA was newly diagnosed in 87 individuals and 5 people had known OSA [64]. OSA was more prevalent in individuals with overweight (60%) and obesity (61%) compared to those with normal weight (32%). A similar prevalence rate of OSA in adults with type 1 diabetes (52%) was reported in a meta-analysis of four studies [62]. Neuropathy may be a risk factor for OSA in type 1 diabetes, as neuropathy may compromise upper-airway reflexes and control of the pharyngeal dilator muscles, which might increase the risk of obstructive events [65].

Type 2 diabetes and insomnia

Insomnia is more common in people with type 2 diabetes than those without diabetes [66]. Insomnia could also be an important risk factor for type 2 diabetes [67] and this risk is stronger when short sleep duration is present [68, 69]. A meta-analysis of prospective cohort studies found that the insomnia symptoms associated with the highest risk of developing type 2 diabetes were difficulty in initiating sleep and difficulty in maintaining sleep, with relative risks of 1.57 (95% confidence interval [CI] 1.25 to 1.97, $p<0.0001$) and 1.84 (95% CI 1.49 to 2.43, $p<0.0001$), respectively [70]. A recent cross-sectional study reported an association between insomnia and type 2 diabetes, and the association remained after adjusting for covariates such as age, sex, smoking, body mass index (BMI), alcohol consumption, other disease history, and depression [71]. Individuals with type 2 diabetes were twice as likely to have self-reported insomnia than individuals without type 2 diabetes. Once stratified by age, the middle-age group had the strongest association between insomnia and diabetes status, followed by the older-age group.

Type 2 diabetes and sleep apnoea

Reviews that have pooled type 2 diabetes risk in people with OSA have provided evidence identifying OSA as an independent risk factor for diabetes development [72, 73]. A recent meta-analysis used a dose–response analysis to suggest that the risk of type 2 diabetes is 40% higher in individuals with OSA [74]. This study also found a linear association, with an 8% increase in risk of type 2 diabetes for each 5-events/h increase in the apnoea–hypopnoea index, an indicator of OSA severity. OSA severity has been associated with measures of hyperglycaemia in type 2 diabetes, after

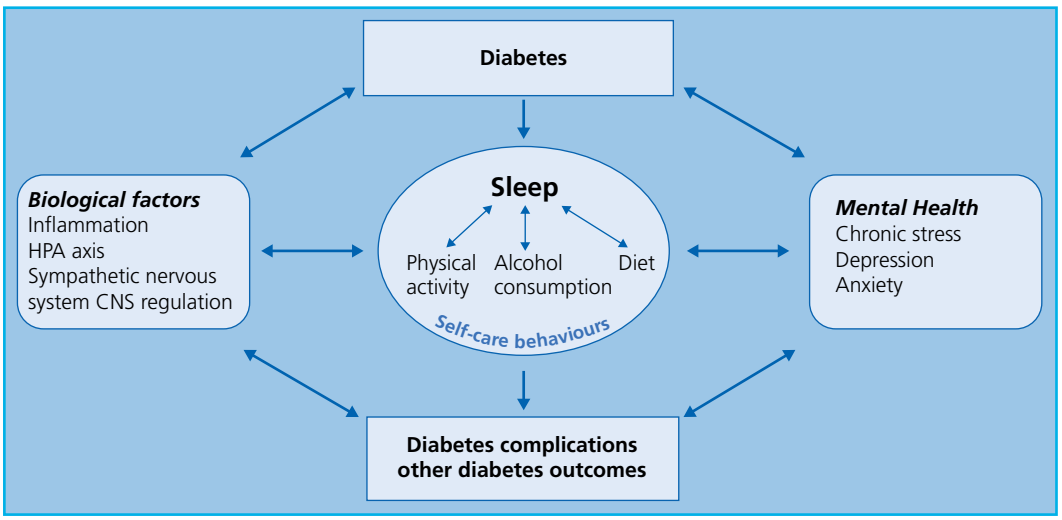

Figure 62.1 The multifaceted relationship between sleep and diabetes and its complications. CNS, central nervous system; HPA axis, hypothalamic–pituitary adrenal axis.

controlling for age, sex, BMI, race, number of diabetes medications, sleep duration, level of exercise, and diabetes duration [75]. People with type 2 diabetes have been found to have higher HbA_{1c} levels by 0.72% (8 mmol/mol; p <0.001) if they have severe OSA than if they do not have OSA [76]. The relationship between CSA and diabetes is less understood [77].

Sleep apnoea is independently associated with insulin resistance and impaired glucose tolerance [78, 79]. Sleep apnoea leads to hypoxia (i.e., lack of oxygen to part of the body), which is implicated in insulin resistance, and this, along with sleep fragmentation, is potentially a pathway to type 2 diabetes in sleep apnoea [80, 81]. A recent meta-analysis determined that there is insufficient evidence to support the hypothesis that sleep apnoea increases the risk of diabetes merely through the common risk factor of obesity [74]. When they excluded studies without BMI or body fat percentage adjustment, the risk remained. Only one of the included studies further examined the role of obesity in this association and found that sleep apnoea was a risk factor for type 2 diabetes in individuals both with and without obesity, suggesting that sleep apnoea increases the risk of diabetes through other mechanisms as well as obesity [74]. Additional studies are needed to examine how variability in BMI plays a role in the association between sleep apnoea and type 2 diabetes.

Type 2 diabetes and sleep duration

The link between short sleep duration and incident diabetes has been supported with evidence from meta-analysis: less than six hours of sleep per night is associated with an approximate 30% increased likelihood of developing type 2 diabetes, compared with seven hours of sleep per night [7]. However, this relationship is a U-shaped one, with both long and short sleep duration contributing to the risk of type 2 diabetes [70, 82, 83]. Sleeping seven to eight hours per day has been associated with the lowest risk of type 2 diabetes [84].

From studies examining the effects of sleep duration on health outcomes among healthy individuals, we can elucidate the possible mechanisms through which sleep duration contributes to diabetes risk. Restricted sleep has been shown to reduce insulin sensitivity and increase insulin resistance in healthy individuals [85, 86]. Long sleep duration has been associated with higher insulin resistance and higher insulin and glucose values in an oral glucose tolerance test in people without diabetes, and these associations remained statistically significant after adjusting for age, sex, family history of diabetes, and other confounding factors (such as obesity, depression, and physical activity), and after excluding participants with severe sleep apnoea and insomnia [87].

Type 2 diabetes and sleep timing and consistency

Only a few studies have examined the association of sleep timing and consistency with diabetes [50]. Results from a cross-sectional study suggested that one-hour increments in sleep duration were inversely associated with type 2 diabetes, while each one-hour increment in sleep variability was positively associated with type 2 diabetes [88]. An earlier study came from the Nurses' Health Study, which followed approximately 70 000 women aged 42–67 years (NHS I, 1988–2008), and 107 915 women aged 25–42 years (NHS II, 1989–2007) without diabetes for a period of approximately 20 years [49]. Duration of shift work was associated with an increased risk of type 2 diabetes in both cohorts, with the women who had been rotating night-shift work for more than 20 years being at the highest risk for type 2 diabetes with a hazard ratio (HR) of 1.58 (95% CI 1.43 to 1.74, p value for trend <0.001). Similarly, another study in women reported an association between greater bedtime variability and insulin resistance, even after adjusting for sleep duration [89]. This study did not focus on shift workers but rather measured four qualities of sleep timing: mean bedtime, bedtime variability, bedtime delay, and bedtime advance. Their findings provide evidence that it is not necessarily shift work that causes the changes that place individuals at risk for metabolic conditions and diabetes, but rather the associated disruption to sleep timing and consistency. However, the existing literature examining the association between sleep timing and consistency and diabetes has produced inconsistent findings, and more research is needed to better understand this relationship [50].

Type 2 diabetes, sleep problems, and depression

Depression is a highly comorbid condition in type 2 diabetes [90] and has been classified as an important risk factor for complications and disability in people with type 2 diabetes [91]. Sleep difficulties (i.e., insomnia and hypersomnia) are diagnostic symptoms for mania and depression [92] and depression is often accompanied by impairments in sleep quality or duration [93]. Depression and sleep problems might interact with each other and increase the risk of diabetes complications in a synergistic way. A prospective large-scale community study found that depression and diagnosed sleep disorders or long sleep duration were independent risk factors for heart disease and were associated with a stronger risk of heart disease when occurring together [94]. Health behaviours (e.g., smoking and physical inactivity) and biological pathways (e.g., chronic inflammation and alterations in hypothalamic–pituitary–adrenal activity) may explain the associations between depression symptoms, sleep problems, and the onset of heart disease [94]. Given that heart disease is a common complication of type 2 diabetes [95], and that those with type 2 diabetes are more vulnerable to depression [90] and sleep problems [93], these findings might be exacerbated among those with type 2 diabetes. However, further research is needed to examine the interactions between sleep and depression in type 2 diabetes.

Type 2 diabetes, sleep duration, and mortality

Wang and colleagues [96] evaluated data from the National Health Interview Survey and found a J-shaped association between sleep duration and all-cause mortality risk in people with type 2 diabetes. Compared with the reference group (7 hours' sleep per day), both longer and shorter durations were associated with increased risk of all-cause mortality: ≤5 h/d: HR 1.24 (95% CI 1.09 to 1.40); 6 h/d: HR 1.13 (95% CI 1.01 to 1.28); 8 h/d: HR 1.17 (95% CI 1.06 to 1.30); ≥10 h/d: HR 1.83 (95% CI 1.61 to 2.08). The association was more prominent in those with a younger age at type 2 diabetes onset and those receiving treatment with both oral glucose-lowering medication and insulin. They suggested that this population may benefit from targeted sleep-related interventions to reduce the risks of adverse health outcomes.

Type 2 diabetes, sleep disorders, and cardiovascular outcomes

A meta-analysis reported that the pooled prevalence of hypertension among individuals with type 2 diabetes and diagnosed sleep disorders was 89% (95% CI 81% to 97%), while the pooled prevalence of hypertension among individuals with type 2 diabetes without diagnosed sleep disorders was 82% (95% CI 80% to 84%) [55]. Hermans et al. [97] evaluated the association between OSA and cardiovascular events and coronary artery diseases in men with type 2 diabetes. The prevalence of cardiovascular events and

coronary artery diseases in men with type 2 diabetes and OSA (61% and 44%, respectively) was significantly higher compared to men with type 2 diabetes without OSA (38% and 27%, respectively). The same study reported that the prevalence of stroke was 15% in men with type 2 diabetes and OSA compared to a prevalence of 8% for men with type 2 diabetes and no sleep disorder.

Type 2 diabetes, sleep disorders, and renal function

There is evidence for a potential relationship between sleep and renal function in people with type 2 diabetes. One study reported a prevalence of 43% for albuminuria and 53% for microalbuminuria among people with type 2 diabetes and comorbid OSA, compared to a prevalence of 34% for albuminuria and 38% for microalbuminuria for those with type 2 diabetes without comorbid OSA [98]. Farghaly et al. reported that people with type 2 diabetes and sleep apnoea had significantly higher serum urea and creatinine levels (7.25 mmol/l and 80.7 µmol/l, respectively) compared to those with type 2 diabetes without sleep apnoea (4.37 mmol/l and 59.0 µmol/l, respectively) [99].

Type 2 diabetes, sleep disorders, and neuropathy

A meta-analysis of 11 studies with 1842 individuals found that OSA was not correlated with neuropathy in people with type 2 diabetes [100]. However, there was significant heterogeneity that might have affected the results. In contrast, the authors found an association between OSA and neuropathy in people with type 1 diabetes. Painful diabetic peripheral neuropathy has been associated with sleep impairment [19, 20].

Type 2 diabetes, sleep disorders, and retinopathy

A cross-sectional study evaluated the association between OSA and the presence and severity of diabetic retinopathy in a sample of 317 individuals [101]. It found an increased risk of diabetic retinopathy in people with severe OSA (odds ratio 2.18, 95% CI 1.14 to 4.18), whereas individuals with mild to moderate OSA were not at an increased risk of diabetes-related eye complications. The authors concluded that those with both severe OSA and type 2 diabetes should be identified as higher-risk individuals in the clinical setting. An association between OSA and advanced diabetic retinopathy was also reported in two UK-based studies [102, 103].

Sleep and diabetes self-management

One of the ways in which sleep disturbance may be linked to diabetes outcomes is via less effective diabetes self-care behaviours, which are vital for diabetes management and prevention of complications. Sleep disturbance may be a critical barrier to proper diabetes self-care and self-management regimens in type 2 diabetes and type 1 diabetes.

In a study of adults with type 2 diabetes, poor self-reported sleep quality was associated with suboptimal diabetes self-care behaviours, assessed by self-reported items related to diet, exercise, and medication taking, with a medium effect size ($r = -0.21$). This study also found a similar association between poor sleep quality and a less healthy diet, which included deviating from meal plans suggested by healthcare providers [104]. In another study of adults with type 2 diabetes, those self-reporting insomnia symptoms had significantly worse diabetes self-care behaviours than those reporting no insomnia symptoms [105]. One study, using actigraphy-measured sleep over eight days in adults with type 2 diabetes, found that more awakenings at night, in addition to fatigue and daytime sleepiness, were associated with suboptimal self-reported diabetes self-management [106]. Sleep continuity disruptions may impair self-regulatory capacities and thus lead to poorer diabetes self-management [106].

Fewer studies are available on sleep and diabetes self-management in paediatric samples and in those with type 1 diabetes [107]. However, disturbed sleep, including poor sleep quality and duration, is associated with suboptimal diabetes self-management in youths and adults with type 1 diabetes. For instance, in a study of 159 adolescents with type 1 diabetes, short sleep durations and lower self-reported sleep quality were associated with a lower frequency of blood glucose monitoring [108]. McGonough et al. examined the associations between self-management regimens and sleep according to daily diary ratings over two weeks in adolescents with type 1 diabetes [109]. Short sleep duration on one night corresponded to a reduced frequency of blood glucose self-monitoring on the following day. In a two-week daily diary sleep study of 236 adolescents with type 1 diabetes, impaired perceived sleep quality was associated with poorer self-regulation around blood glucose self-monitoring [110]. Similar findings were reported in a study of adults with type 1 diabetes [111]. However, long sleep duration may also play a role. One study of adolescents with type 1 diabetes found that those who slept longer hours were less likely to follow self-management regimens and undertake blood glucose monitoring [112]. Therefore, both short and long sleep may disrupt diabetes self-management behaviours, though further research from prospective cohort studies is needed.

Excessive daytime sleepiness may be an explanation for these associations. In a sample of veterans with type 2 diabetes from the USA, there was a 21% increased odds of sedentary activity for those self-reporting daytime sleepiness [113]. Notably, however, sedentary activity was defined as walking <150 min/wk, and thus only physical activity related to walking was measured.

Increased emotional eating may also play a role, as this behaviour is associated with poor sleep quality and fatigue in adults with type 2 diabetes [114]. As evidence from the general population additionally suggests that unhealthy diets and low physical activity are linked with sleep disturbance [115], a reciprocal pattern of associations between sleep and health behaviours may best characterize people with diabetes. For instance, findings from a five-year prospective cohort study in middle-aged and older adults from the USA suggest that higher levels of weekly physical activity were associated with a lower risk of polysomnography-assessed sleep disturbances [116]. However, the bidirectional and potential reciprocal associations between sleep and diabetes self-management behaviours, to date, have not been directly investigated.

Depression may be another potential mechanism linking sleep disturbance with difficulties in diabetes self-management. Depression is associated with short and long sleep durations [93]. Sleep disturbance is a symptom of a major depressive disorder according to diagnostic criteria [29], and sleep disturbance is associated with the incidence of depressive symptoms [117]. Depression is also associated with suboptimal diabetes self-care behaviours [118-120]. Therefore, depression might mediate the association between sleep disturbance and diabetes self-management behaviours, though this has not been directly examined. There may also be a synergistic interaction between the combination of depression and sleep disturbance, with depression potentially acting as a catalyst leading to worse diabetes self-management. Depression may enhance the effect of sleep disturbance on diabetes self-management through

impaired glucose measures and fatigue. There could additionally be bidirectional effects, where sleep disturbance influences poor diabetes self-management, and where suboptimal diabetes self-management and sleep disturbance [121] may lead to metabolic changes that are linked with the incidence of depression [122]. The relationship between sleep disturbance, depression, and diabetes self-management is likely to be complex. Addressing depression and related mental health factors such as diabetes distress in individuals with sleep disorders might play an important preventive role in terms of diabetes management, though further research is needed.

Several knowledge gaps remain in understanding the role that sleep disturbance plays in the behaviours that are needed to optimize diabetes self-care, and these gaps may stem largely from the lack of prospective cohort studies examining these associations with large samples of people with type 1 diabetes and type 2 diabetes. Several putative mechanisms may explain the associations between sleep disturbance and less effective diabetes self-management regimens, but the formal tests of mediation in prospective cohort studies that are necessary to better understand the nature of this association are lacking. Despite these limitations, there is evidence to suggest that sleep disturbance in people with type 1 diabetes and type 2 diabetes can impede efforts at optimal diabetes self-management, and therefore that addressing sleep disturbance as part of the clinical management of diabetes may be beneficial.

Clinical implications

Diabetes healthcare professionals can screen for sleeping problems using brief questionnaires during routine care appointments. For example, the Patient-Reported Outcomes Information System (PROMIS) Sleep Disturbance Scale [123] is a brief six-item measure that assesses sleep disturbance over the past seven days. This tool, which can be completed either online ahead of an appointment or during an appointment, can help healthcare professionals working with people with diabetes to identify sleep problems. If a person has a positive screen for sleep disturbances, then a more comprehensive assessment could follow, including the Pittsburgh Sleep Quality Index [23].

Minor sleep issues can be addressed directly with brief psychosocial interventions conducted by healthcare professionals, such as promoting and educating on sleep hygiene. Individuals with moderate to severe sleep disturbances could be referred to appropriate specialists, who might include psychologists, psychiatrists, and other sleep and behaviour specialists. Individuals with sleep disturbances should be reassessed for sleep disturbance and diabetes management difficulties more frequently. Otherwise, screening should take place yearly as part of regular diabetes care. Finally, we recommend that sleep should not be considered in isolation, as there could be important interactions with other symptoms and conditions, such as depression.

Conclusion

The relationship between sleep and diabetes is complex: sleep impairments seem to be both affected by, and risk factors for, diabetes and its complications, while also being a barrier to effective diabetes self-management. People with diabetes may benefit from the screening of sleep problems to avoid adverse cycles of the behavioural, physiological, and mental health effects of poor sleep on health and well-being. Given the high prevalence of sleep-related problems in type 1 diabetes and a strong link between OSA and markers of glucose metabolism, identification, and evaluation of sleep problems and disorders in people with type 1 diabetes may facilitate diabetes management and glycaemic levels. The epidemiology of sleep disorders in type 1 diabetes and its relation to glycaemic indices require further examination. Future research should aim to focus on isolating the role of individual sleep disorders in type 2 diabetes from sleep duration and clarifying the contribution of sleep consistency and timing. A clearer understanding of the role of obesity and depression in the sleep–diabetes relationship is warranted. Longitudinal studies using objective sleep assessments are needed to clarify the role of sleep in the development of diabetes complications and its interaction with behaviour and mental health comorbidities.

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10 Psychosocial Aspects of Diabetes

63 Psychosocial and Behavioural Aspects of Diabetes

Frans Pouwer[1,2,3] and Jane Speight[1,3,4]

[1] Department of Psychology, University of Southern Denmark, Odense, Denmark
[2] Steno Diabetes Center Odense (SDCO), Odense, Denmark
[3] Department of Medical Psychology, Amsterdam UMC, Amsterdam, The Netherlands
[4] Australian Centre for Behavioural Research in Diabetes, Diabetes Victoria, Melbourne, Victoria, Australia

Key points

- Both type 1 diabetes and type 2 diabetes can affect psychological well-being and quality of life. In most instances, these effects are modest and are most likely to be associated with certain adverse events that occur during the course of diabetes or its management.
- Diabetes-specific distress and fear of hypoglycaemia are both common among people with diabetes.
- For most people with diabetes, generic health status and health-related quality of life do not differ markedly from people with other chronic conditions, such as arthritis. Lower health-related quality of life is associated with diabetes complications, being female, physical inactivity, low income, and recurrent hypoglycaemia.
- Diabetes-specific quality of life can be impaired by intensive diabetes management, hypoglycaemia, and complications. It can be improved with flexible approaches to intensive treatment.
- Diabetes-related stigma is common. This includes perceived or experienced judgement, blame, rejection, exclusion, and discrimination due to diabetes. Sources of stigma include the media, general public, family, and health professionals and this can be internalized as self-stigma. It is apparent that the way in which we communicate about diabetes (the language and imagery used) can fuel or reduce diabetes stigma. Diabetes stigma is associated with impaired psychological well-being, diabetes self-care, and quality of life, and less frequent healthcare access. Diabetes stigma should be countered wherever it occurs.
- Psychological factors contribute to the risk of developing type 2 diabetes; these include adverse childhood experiences, chronic stress, high job strain, low stress resilience, insomnia, depression and anxiety disorders, and schizophrenia. The mechanisms remain poorly understood.
- Around 50% of type 1 diabetes is diagnosed in childhood, but children show remarkable psychological resilience to the diagnosis. About one-third report some psychological distress shortly after diagnosis, but this generally subsides within six months. Problematic adjustment is characterized by increased depressive symptomatology, more anxiety, social withdrawal, and sleep disturbances. A similar adjustment reaction is often seen in parents, particularly mothers, of children with newly diagnosed type 1 diabetes. Diagnoses of post-traumatic stress disorder are also more common in parents, occurring at rates comparable with those reported among parents of children diagnosed with cancer.
- During the first 5–10 years of living with type 1 diabetes, most children and adolescents have adequate psychological functioning; however, after 10 years, rates of anxiety, depression, and eating disorders increase markedly, with as many as one-third of adolescents with diabetes meeting the criteria for one or more psychiatric disorders. Diabetes distress is more common in adolescence than at any other life stage.
- Macrovascular disease, chronic foot ulceration, and proliferative retinopathy increase the risk of psychopathology, an understandable reaction to serious complications; however, lifetime psychiatric disorders such as depression may also increase the risk of later development of both macrovascular and microvascular complications. Recurrent diabetic ketoacidosis, particularly in young women, is also predicted by psychological problems such as disordered eating, and by high rates of family dysfunction.
- Diabetes management and health outcomes are influenced by reciprocal relationships between glycaemic levels and psychological variables. The latter include enduring psychological traits such as locus of control, coping style, temperament, and transitory psychological states (stress, anxiety, depression). Diabetes outcomes are also strongly related to family functioning, especially in children and adolescents: low family conflict, good communication, cohesion, and marital satisfaction relate to more optimal glycaemic outcomes.
- Self-care behaviours (medication taking, glucose monitoring, healthy eating, physical activity) are only weakly related to glycaemic outcomes. This may reflect the inaccuracy of self-reported behaviours, the crudeness of the self-report measures, the discrepancy between *typical* recent behaviours (e.g. past two weeks) and glycated haemoglobin (HbA_{1c}, a measure of the average blood glucose over the past 8–12 weeks), or the inherent complexity, relentlessness, and challenges of manual self-management of diabetes.
- Several interventions are effective in improving psychological well-being. These include individual or group therapy, counselling based on the

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principles of cognitive behavioural therapy (CBT), or mindfulness-based therapies and web-based CBT, as well as psychotherapy and family therapy.
- Other interventions, effective for improve psychological well-being, self-care, and health outcomes, include empowerment-based approaches and structured training or education programmes. The components of effective programmes include (with varied emphasis) goal-setting, problem-solving, coping, managing stress, self-motivation, and self-management skills.

Diabetes and psychology have long been linked: Areteus of Cappadocia (first or second century) described life with diabetes as 'disgusting and painful'. In the seventeenth century, Thomas Willis mentioned long grief and melancholia as potential causes of diabetes. More than three centuries later, a meta-analysis of modern longitudinal epidemiological studies confirmed that Willis was right. This chapter examines five major themes:
- Psychological risk factors for diabetes.
- Psychological impact of living with diabetes and its complications.
- Impact of psychosocial factors on diabetes self-management.
- Impact of behaviour on diabetes management.
- Interventions to reduce psychological distress and improve self-care, glycaemic outcomes, and quality of life.

Psychological risk factors for developing diabetes

A range of psychiatric and psychological risk factors for type 2 diabetes has been investigated. An umbrella review of 25 systematic reviews of longitudinal epidemiological studies showed that several psychiatric conditions are associated with increased risk of developing type 2 diabetes [1]. The following psychiatric disorders and treatments were associated with an increased risk of incident type 2 diabetes:
- Treatment with antipsychotic medication (odds ratio [OR] 1.93–1.94).
- Insomnia (relative risk [RR] 1.55–1.74).
- Depression (RR 1.18–1.60) and anxiety disorders (OR 1.47).
- Treatment with antidepressant medication (RR/OR 1.27–1.50).

Chapter 65 provides further details on the relationship between common mental disorders and severe mental illness and an increased risk of developing type 2 diabetes.

Psychological risk factors for type 2 diabetes

Several psychological risk factors have been linked to an increased risk of type 2 diabetes. These include general emotional stress, job stress, adverse events in childhood, sleeping problems, anger, and hostility [1–3]. Using data from over 9000 participants in the British Household Panel Survey, Mommersteeg et al. [4] found that, compared to adults reporting a low level of psychological distress, those with higher levels were at a 33% increased risk of developing type 2 diabetes during the 18-year follow-up. Additional analyses showed that this association might be mediated by a low energy level and impaired health status. Both sleep quality and quantity (too much and too little) predict the onset of type 2 diabetes. In a systematic review of 10 longitudinal studies, involving >107 000 men and women without diabetes at baseline [5], short sleep duration (≤5–6 h/night) increased diabetes risk by 28%, while long duration (>8–9 h/night) increased risk by 48%; difficulty in initiating and maintaining sleep increased diabetes risk by 57% and 84%, respectively [5]. A systematic review of nine longitudinal studies showed that high baseline job strain (high job demands and low control) was associated with a 16% higher risk of incident type 2 diabetes compared with no job strain (all other combinations), particularly in women (RR 1.48) [6]. Another systematic review investigated whether adverse childhood experiences were associated with a higher diabetes risk. The review included four cohort studies and three cross-sectional investigations. Adverse childhood experience was positively associated with a 32% increased risk of type 2 diabetes. The association was strongest for neglect (pooled OR 1.92) and less strong for sexual abuse (OR 1.39) and physical abuse (pooled OR 1.30) [7]. Chronic emotional stress is common in individuals with a psychiatric condition and might be an important common denominator for the elevated risk for type 2 diabetes.

Most studies have focused on emotional problems or psychological factors as transient states, such as current depression or stress levels. However, if psychological factors have an impact on the development of type 2 diabetes, this is most likely a process over several years. Therefore, personality factors or traits may also play an important role. The role of stress resilience in the onset of type 2 diabetes was investigated prospectively in a national cohort study of 1.5 million male military conscripts in Sweden (from 1969 to 1997) with follow-up over 25 years (from 1987 to 2012) [8]. Stress resilience was assessed using a *gold standard* interview by psychologists (with high inter-rater reliability). Controlling for family history of type 2 diabetes and baseline body mass index, those with low stress resilience were 51% more likely to be diagnosed with type 2 diabetes than those with a greater ability to cope with stress [8]. Chronic stress was associated with a number of unhealthy behaviours (e.g. physical inactivity, unhealthy diet, sleep problems, smoking) as well as activation of the innate immune system (increased interleukin 6 and other cytokine mediators of stress response, which may mediate insulin resistance). A recent systematic review of 10 longitudinal and 13 cross-sectional studies investigated whether various personality characteristics are associated with having, or the risk of developing, metabolic syndrome, but there is conflicting evidence for high hostility, neuroticism, or type D (distressed and socially inhibited) personality as risk factors, possibly reflecting publication bias [9]. Consequently, we need new epidemiological cohort studies with a prospectively published study protocol to further our knowledge about the role of chronic emotional stress, depression and anxiety, and personality traits as risk factors for the development of type 2 diabetes. One example is the Maastricht Study [10], which will investigate not only depression and anxiety, but also various personality factors in relation to type 2 diabetes. Future research also needs to focus on identifying behavioural and physiological mechanisms linking various forms of stress and incident type 2 diabetes.

Psychological risk factors for type 1 diabetes

Psychological stress might be an environmental risk factor for type 1 diabetes. The incidence of type 1 diabetes is increasing by 3–5% per year [11] and researchers are investigating both psychological and environmental risk factors to explain this increase. In their

recent review, Ilchmann-Diounou and Menard [12] hypothesize a role of stress-induced intestinal barrier disruption in the development and/or course of different autoimmune diseases, including type 1 diabetes, multiple sclerosis, and systemic lupus erythematosus. A population-based study comparing 67 young people (aged 0–14 years) with type 1 diabetes and 61 age-matched people without type 1 diabetes showed that type 1 diabetes was more commonly associated with a history of negative life events in the first two years of life, life events with difficult adaptation, child behavioural deviances, and more chaotic family functioning [13]. In the prospective All Babies In southeast Sweden (ABIS) study, 58 out of 10 495 children developed type 1 diabetes, with childhood experience of a serious life event being associated with higher risk (hazard ratio [HR] 3.0; 95% confidence interval [CI] 1.6 to 5.6) [14]. Using register-based data covering all children (>2 million) born in Denmark between 1980 and 2015, Bengtsson et al. found that a larger number of adversities in childhood had a significant but small effect on the risk for type 1 diabetes among women (adjusted HR per adversity increase: 1.07), but not among men (adjusted HR per adversity increase 0.99) [15]. However, caution is needed, because observational data often come with important methodological problems such as selection bias and recall bias. Furthermore, multiple issues can arise in the analytical stage, such as residual confounding and multiple testing error [16].

Psychosocial impact of living with diabetes and its complications

Psychological distress shortly after diagnosis

The term psychological distress refers not only to depressive and anxiety symptoms, but also to diabetes-specific distress. Depression and anxiety are both common mental disorders, while diabetes-specific distress reflects a person's negative emotional response to the burden of living with diabetes, not the presence of a psychiatric condition [17]. Depression, anxiety, and diabetes-specific distress partly overlap, but are not interchangeable constructs.

People with diabetes live with a condition that can shorten their life expectancy, can lead to debilitating complications (e.g. blindness or neuropathy), and requires them to take daily responsibility for managing their condition (e.g. with medications or insulin injections, healthy habits, and careful monitoring of glucose levels) for the remainder of their lives.

Children and their parents

In contrast to expectation, children and adults show remarkable psychological resilience to a diagnosis of diabetes. In what may be the most comprehensive prospective psychological study of children with type 1 diabetes and their families, Kovacs et al. [18] assessed 95 children, 8–13 years of age, shortly after discharge from their initial hospitalization, and followed them for 6–10 years. Within three months of diagnosis, 36% of the children experienced sufficient psychological distress to meet criteria for a diagnosable psychiatric disorder [19]. Most had *adjustment disorder*, defined as a transient reaction that exceeds the normal and expected response to a stressor, which develops within three months of onset of the stressor and lasts no more than six months. The occurrence of such a disorder signals that the child is beginning to come to terms with the diabetes, and can be considered a component of the *mourning process* that often accompanies the development of any chronic illness [20]. As expected, recovery was rapid, with 93% showing complete remission of psychiatric symptoms within nine months.

Greatly elevated rates of post-traumatic stress disorder (PTSD) have been reported in a prospective study of parents evaluated at 6 weeks, and 6 and 12 months after their child's diagnosis. Depending on the time point, 16–22% of mothers and 8–14% of fathers met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for a PTSD diagnosis [21]. These rates were significantly higher than symptoms in the general population, but are comparable with those seen in mothers of children diagnosed with cancer. The best predictor of PTSD severity at 12 months was PTSD severity at 6 months; episodes of hypoglycaemia were also associated with an increased severity of PTSD.

Adults

The onset of type 1 diabetes during adulthood ought to produce similar adjustment disorders within several months of diagnosis in both the individual and partners or close family members. A German study used structured interviews that provided diagnoses according to DSM-IV in a sample of adults (aged 17–40 years) with newly diagnosed type 1 diabetes and compared them with a large reference group, comprising a representative population of 2046 persons of a similar age. People with type 1 diabetes had a rate of major depressive episodes twice that of the reference group (5.8% vs 2.7%) [18]. A more careful analysis showed that these differences were statistically significant only for women with type 1 diabetes (9.3% vs 3.2% in the reference group), with no differences in men (3.6% vs 2.2%) nor for other psychiatric disorders [22]. Studies of adults with type 2 diabetes report mixed findings regarding psychological morbidity in the first year following diagnosis. Interestingly, in the Anglo-Danish-Dutch study of intensive treatment in people with screen detected diabetes in primary care (ADDITION), screening for type 2 diabetes and a subsequent diagnosis of type 2 diabetes had limited psychological impact on newly diagnosed individuals compared to those without diabetes [23]. A meta-analysis demonstrated the prevalence of depression to be higher in adults with diagnosed type 2 diabetes compared to those with undiagnosed type 2 diabetes, impaired glucose metabolism, or normal glucose metabolism [24]. The recent LifeLines study was a large epidemiological study of 90 686 participants who underwent diagnostic psychiatric interviews and had fasting glucose levels measured [25]. In contrast with the earlier meta-analysis [19], LifeLines showed that depression was independently associated with type 2 diabetes, both diagnosed (OR 1.4 [95% CI 1.1 to 1.8]; $p = 0.006$) and undiagnosed (OR 1.8 [95% CI 1.3 to 2.6]; $p = 0.001$), while anxiety is independently associated with diagnosed type 2 diabetes (OR 1.4 [95% CI 1.2 to 1.7]; $p < 0.001$) but not undiagnosed type 2 diabetes [25]. A smaller clinical study of 71 participants reported that >50% expressed no emotional reaction to the diagnosis and felt that they could cope [26].

Psychological reactions emerging in the course of diabetes

Living with and managing diabetes are a complex endeavour. People with type 1 diabetes or insulin-treated type 2 diabetes must take responsibility for administering insulin doses and checking glucose levels (often several times per day), carefully monitoring food intake and physical activity, and then readjusting insulin, food, and/or exercise in response to high or low glucose values or during acute illness. For those with type 2 diabetes not using insulin, the treatment regimen can be less onerous, but adopting and

sustaining healthy lifestyle behaviours can also be burdensome, and having to adjust diet and physical activity to improve outcomes can be frustrating and demoralizing. In either instance, people with diabetes and their families assume primary responsibility for these self-care behaviours, all of which are directed at achieving or maintaining optimal glycaemic levels and quality of life.

Psychological impact among children and adolescents with diabetes

Most children and adolescents with type 1 diabetes function well psychologically as the diabetes progresses, although there may be small increases in depressive and anxiety symptomatology and internalizing behaviours, such as somatic complaints, social withdrawal, and sleep disturbance. In school-aged children [27] this is evident after two to three years of type 1 diabetes, yet the magnitude of these changes does not reach clinically significant psychopathology. Somewhat higher rates of externalizing, or aggressive, behaviours have also been reported, with this phenomenon especially pronounced in boys [27], and strongly associated with persistent hyperglycaemia [28].

Children who report more difficulties in managing their type 1 diabetes also show more symptoms of psychological distress. Levels of psychological distress shortly after type 1 diabetes onset are often a good predictor of psychological problems later [29]. This suggests that it is helpful to assess psychological well-being shortly after diabetes onset and to monitor this routinely thereafter; the utility of monitoring psychological well-being in adolescents with diabetes, for example with the MIND Youth Questionnaire (MY-Q), was confirmed in a randomized controlled trial (RCT) [30, 31]. The frequency of assessments can be adjusted to the needs of the young person with diabetes, and intensified where indicated to guide further clinical actions and initiate stepped care [32].

Disordered eating is a common and clinically relevant problem in young people with diabetes. In a national survey among Danish adolescents with type 1 diabetes, approximately one-third of participants had overeating or binge eating symptoms [33]. Symptoms of binge eating were associated with elevated depression, lower quality of life, higher anxiety, and worse clinical outcomes. Disordered eating and insulin omission are common problems in diabetes, which are frequently overlooked and associated with less optimal glycated haemoglobin (HbA_{1c}) [34].

Marked elevations were found in rates of psychiatric disorder when assessed by a structured psychiatric interview. Not only were girls more often affected than boys [35, 36], but their risk for recurrence of depression was greater. In a cohort of Australian children with newly diagnosed type 1 diabetes assessed over a 10-year period, 37% had at least one DSM-IV diagnosis [35]; of those, 60% met criteria for two or more disorders and 55% met criteria for three or more disorders [35]. Each of mood, anxiety, and eating disorders was present in 17% of the sample and nearly 20% manifested a behavioural disorder. Those adolescents who met criteria for a DSM-IV psychiatric disorder were also more likely to have manifested significant externalizing problems shortly after diagnosis, which were likely to have preceded diagnosis. Maternal psychopathology is a potent predictor of subsequent psychiatric disorder and increased depressive symptomatology in children and adults with type 1 diabetes [37].

Elevated rates of suicidal ideation have been reported for adolescents with type 1 diabetes, with lifetime prevalence rates of ~26% compared to 9–12% for adolescents without diabetes [38]. Although the rate of actual suicide attempts is low among young people with diabetes (4%), suicidal ideation was associated with greatly increased rates of disengagement from medical treatment.

Relatively little is known about diabetes-specific distress in children and adolescents. Largely this is due to the dearth of appropriate measures for this age group and lack of recognition, until recently, of the potentially important role of diabetes-specific distress. A recent systematic review [39] highlights that only three measures have been developed specifically for adolescents and the prevalence of clinically relevant diabetes-specific distress is estimated to affect around one-third of adolescents. Diabetes distress appears to be associated with higher HbA_{1c} (particularly when age-appropriate measures of diabetes distress are used), although associations with self-care behaviours were mixed [39]. While parental emotional support appears to be associated with lower rates of diabetes-specific distress, neither age nor gender appears predictive of diabetes-specific distress [39]. Importantly, diabetes-specific distress is strongly associated with depressive symptoms [39], suggesting that these constructs are inter-related and perhaps that interventions to reduce diabetes-specific distress may improve the general well-being of adolescents with diabetes.

The International Society for Pediatric and Adolescent diabetes (ISPAD) consensus guidelines [40] emphasize that 'Mental health professionals should be available to interact not only with patients and families at clinic visits to conduct screening and more complete assessments of psychosocial functioning, but also to support the diabetes team in the recognition and management of mental health and behavior problems. There should also be easy access to consulting psychiatrists for cases involving severe psychopathology and the potential need for psychotropic medications. All mental and behavioral health specialists should have training in diabetes and its management.'

Psychological impact among adults with diabetes

The process of psychological adaptation to the diagnosis of diabetes in adulthood remains incompletely understood, largely because few longitudinal studies have been conducted with adults. The Diabetes Control and Complications Trial (DCCT) [41], the largest prospective study of adults with type 1 diabetes, found no change in self-reported psychological symptomatology over a follow-up period of 6–9 years, and found no relationship between type of treatment (conventional or intensive insulin therapy) and levels of psychological distress [42]. In an early systematic review, rates of clinically significant depression were higher in both treatment groups (25%) compared with rates of depressive symptoms (measured by self-report questionnaire) in the general population (14%) [43].

Cross-sectional studies of adults with either type 1 diabetes or type 2 diabetes have demonstrated repeatedly that rates of psychological distress, particularly depressive symptoms and anxiety, tend to be higher than in the general population, but are usually comparable to those reported in individuals with other chronic conditions [44–46]. Using self-report measures of psychological symptoms, Peyrot and Rubin found greatly elevated rates of both depressive (41%) and anxiety symptomatology (49%), with 38% of their entire sample showing elevations in both domains; however, repeated reassessment of these individuals over a six-month period indicated that these effects are quite unstable [47]. Across all three assessments, only 13% of the sample was persistently disturbed. The strongest predictors of ongoing distress included being female, having less than a high school education, being middle-aged, and having more than two diabetes-related biomedical complications [48]. A longitudinal study in individuals with type 2 diabetes

treated in primary care with three-year follow-up found that 26% met the criterion for depression at one or more assessments [49]. Incident depression was present at follow-up in 14% of those without depression at baseline, and 66% reported recurrent or persistent depression during follow-up. The results also clearly showed that the best predictor of future depressive symptoms is a history of depression [49]. A systematic review of 26 studies, mostly involving adults with type 2 diabetes, concluded that there is a bidirectional longitudinal association between depressive symptoms and HbA_{1c}, with small effect sizes [50].

The concept of diabetes-specific distress emerged in the adult diabetes literature over 25 years ago, with the publication of the Problem Areas In Diabetes (PAID) scale [51]. There was no significant difference in diabetes distress scores among those with type 1 diabetes or insulin-treated type 2 diabetes, and scores were only weakly associated with age and diabetes duration [52]. 60% of study participants reported at least one diabetes-related problem as *serious*, with the top five most frequently endorsed serious problems being:

- Worries about the future and the possibility of serious complications.
- Feeling guilty or anxious when you get off track with your diabetes management.
- Feeling scared when you think about living with diabetes.
- Feeling discouraged with your diabetes regimen.
- Feeling depressed when you think about living with diabetes.

This seminal study also found that diabetes-specific distress was associated negatively with self-care (after adjustment for age, diabetes duration, and general emotional distress) and correlated positively with HbA_{1c}. Various more recent and international studies corroborate these findings [52–54], though it should be noted that few such studies exist in low- to middle-income countries. Elevated diabetes-specific distress is experienced by 20–30% of adults with type 1 diabetes, and is more likely in women and in those with longer type 1 diabetes duration, severe hypoglycaemia, and younger age [55]. While many of the key emotional problems may not discriminate by diabetes type [51], the diabetes distress experienced by adults with type 1 diabetes tends to relate to 'worries about low blood sugar reactions' and 'feeling burned out by the constant effort to manage diabetes', while that experienced by adults with type 2 diabetes relates more to 'not having clear and concrete goals for your diabetes care' and 'feeling constantly concerned about food and eating' [55].

Many studies have focused on diabetes distress, but longitudinal studies remain scarce. For example, we do not know whether elevated diabetes distress is associated with an increased risk of developing long-term diabetes-related complications, and little is known about how diabetes distress develops [56]. It is increasingly apparent that the communication style and (unrealistic) expectations of healthcare professionals may increase the diabetes distress experienced by those with diabetes and contribute to its development [56]. Thus, considerable advocacy efforts now focus on the language (words) used in diabetes to ensure appropriate and realistic communication with and about people with diabetes [57, 58].

Psychosocial impact of diabetes-related complications

Psychological reactions to acute biomedical complications

Acute complications of diabetes include diabetic ketoacidosis (DKA; Chapter 41) and severe hypoglycaemia (Chapter 40), both of which may be rare or recurrent events for an individual, and be influenced by the individual's personal and treatment characteristics.

The frequency of DKA peaks in adolescence, and recurrent DKA remains an issue among only a minority of adults with type 1 diabetes, largely predicted by intentional insulin omission or disordered eating behaviours. Skinner notes that this is because of feelings of depression, resentment, denial, and rebellion against diabetes [59]. Many interventions have potential depending on the person's circumstances: changing insulin regimens (including nurse-led injections, insulin pump), cognitive behavioural therapy (CBT), and family therapy are all options. A recent case–control study confirmed that people with type 1 diabetes and recurrent DKA had higher levels of anxiety or diabetes distress, more difficulties with emotion regulation and higher levels of personality dysfunction [60]. An important step in resolving recurrent DKA is a multidisciplinary approach, with knowledge of the person with diabetes from a psychosocial perspective and, perhaps most importantly, not losing contact with the person experiencing recurrent DKA [59].

Acute hypoglycaemic episodes are often uncomfortable and unpredictable. They are accompanied by autonomic arousal characterized by aversive symptoms such as trembling, sweating, lightheadedness, pounding heart, nervousness, feelings of agitation, and worries that this episode could lead to a seizure, coma, or death if not treated promptly. Thus, the development of fear of hypoglycaemia, and the corresponding effort to avoid any situation that may lead to a recurrence of a hypoglycaemic event, is unsurprising and an adaptive psychological reaction. In the second Diabetes Attitudes, Wishes and Needs (DAWN2) study, conducted in 17 countries, 56% of participants with diabetes reported being worried about hypoglycaemic events [61]. Fear of hypoglycaemia is indiscriminate, occurring in children [62] and adults with diabetes [63, 64], but especially in parents [62] and spouses [65], who can be more fearful than the individual, as they are often more acutely aware of its impact, while the person is unconscious with little recall of the event. In the DAWN2 study, 61% of family members of people with diabetes reported being worried about hypoglycaemia [66].

Adults with type 1 diabetes who experience recurrent hypoglycaemia, or even a single episode of severe hypoglycaemia when accompanied by seizure or coma, have greater fear of hypoglycaemia [67]. This can be accompanied by broader diabetes-specific distress and impaired generic emotional well-being [68]. This is likely to be a consequence of several factors, including pre-existing personality traits, particularly neuroticism or trait anxiety, and current level of psychological distress [69]. Recent work has begun to explore the relationship between fear of hypoglycaemia and risk of severe hypoglycaemia, identifying four subgroups (e.g. low fear/low risk; high fear/high risk; low fear/high risk; high fear/low risk), demonstrating the complexity of such fear and the importance of understanding the nature of the fear for determining suitable clinical interventions [70].

A systematic review including 27 studies in adolescents with type 1 diabetes concluded that severe hypoglycaemia was associated with more worries about hypoglycaemia, but was not clearly associated with diabetes distress, depressive symptoms, anxiety symptoms, or disordered eating or post-traumatic stress disorder [71]. More recent, more frequent, and also more severe episodes of hypoglycaemia were associated with adverse psychological outcomes [71]. Another systematic review of 30 studies in adults with type 1 diabetes reported that there was no association between

hypoglycaemia and diabetes-specific quality of life, but also that severe hypoglycaemia was linked to increased fear of hypoglycaemia and higher levels of diabetes distress, and lower general emotional well-being [72]. No associations with depression, anxiety, or health status were found. Self-treated hypoglycaemia was positively associated with fear of hypoglycaemia. Importantly, none of the included studies had investigated the impact of hypoglycaemia on general quality of life [72]. A recent systematic review of longitudinal studies concluded that (recurrent) hypoglycaemia has a negative impact on quality of life in people with type 2 diabetes [73]. Hypoglycaemia is associated with more depressive and anxiety symptoms, and also with impairments of the ability to drive, work, and function in ways that are important for quality of life [74].

In addition to being associated with higher levels of generalized psychological distress, fear of hypoglycaemia may lead people with diabetes, and parents of children with diabetes, to avoid hypoglycaemia by treating falling blood glucose prematurely and hence maintaining blood glucose at higher than optimal levels [75]. Other, much rarer, diabetes-specific fears include fear of injecting or self-testing [76, 77]; the prevalence of a phobia to needles or blood and injury remains controversial, but is likely between 1% and 10% [76, 77].

Psychological reactions to long-term biomedical complications

Several international studies have now demonstrated that worries about the future and the possibility of serious complications are the foremost *problem areas* for people with diabetes [51–54]. This is unsurprising given that long-term complications (such as retinopathy, neuropathy, nephropathy) can have a devastating impact on the individual's health [78]. Due to the emphasis placed on the importance of managing diabetes optimally to prevent complications, their development may also be viewed by people with diabetes, their families, healthcare providers, and others as a sign that they have *failed* to self-manage the condition adequately. Thus, it is reasonable to consider that the onset of complications leads to psychological distress, due to the emotional impact and significance of a new health status, but also to a change in self-perception or identity and to self-blame and guilt. This conjecture has not been tested empirically and it is unknown how adults react psychologically immediately after a complication appears. A systematic review of 22 longitudinal studies concluded that the relationship between depression and diabetes complications is bidirectional [79]. Depression was a stronger predictor of diabetes complications then vice versa. To date, results from meta-analyses [79] have shown that baseline depression was associated with a higher risk of incident macrovascular (HR 1.38; 95% CI 1.30 to 1.47) and microvascular complications (HR 1.33; 95% CI 1.25 to 1.41). Having diabetes complications was associated with an increased risk of developing depressive disorder (HR 1.14; 95% CI 1.07 to 1.21) [79].

People who develop retinopathy, and with it varying degrees of vision loss, experience a range of adverse social impacts (including social isolation, increasing dependence on others, and disruption to family functioning) as well as an array of emotional impacts (including loss of confidence, fear, vulnerability, anger, stress, and depression) [80]. However, the degree of psychological distress secondary to visual loss may not be unique to people with diabetes; at least one study of older adults has reported no significant difference in psychological adjustment between those with and without diabetes, either at the onset of visual loss or when re-evaluated 12 months later [81].

Social stigma and discrimination

Social stigma is a negative social judgement that can lead to perceived or experienced blame, stereotyping, rejection, exclusion of, or discrimination against, a person or group based on a particular feature. The International Diabetes Federation's (IDF') Global Diabetes Plan 2011–2021 advocates that we must 'challenge social stigma and discrimination in the context of diabetes' [82]. In 2013, the first narrative review focused on this topic [83] showed diabetes stigma to be an underexamined but potentially important issue. In-depth exploratory interview studies focused on diabetes stigma among adults [84, 85] showed that more than 80% of respondents reported (without prompting) that they have experienced some form of diabetes stigma and/or discrimination. This led to the development of two novel diabetes stigma assessment scales (DSAS-1 and DSAS-2) to enable studies to quantify the extent and impact of diabetes stigma [86, 87]. These have shown that 25–67% of respondents have been 'blamed and shamed' for developing diabetes and/or its complications – by family, community, media, and health professionals; 77% of adults with type 1 diabetes and 37% of adults with type 2 diabetes indicate that other people judge them for their food choices; and 26% of adults with type 1 diabetes 'feel embarrassed about what people might think' if they need help with a hypoglycaemic episode, while 31% of adults with type 2 diabetes blame themselves for having type 2 diabetes (self-stigma). Comprehensive assessments of correlates and moderators show that diabetes stigma has diverse negative associations with psychological well-being, diabetes self-management, social support, and seeking healthcare support [88–91].

Collectively, this work shows that stigma adds substantially to the burden of living with diabetes. However, further research is needed urgently to identify effective interventions to reduce diabetes stigma, and to advance our understanding of diabetes stigma among culturally and linguistically diverse populations.

Quality of life

Psychological distress has so far been the primary focus of this chapter, but the extent to which diabetes affects an individual's perceived quality of life is also important. Defining and measuring quality of life remains controversial, although it is generally agreed that it is multidimensional (including physical, psychological, and social domains), subjective (domains will vary in importance and relevance for each individual), and dynamic (changing over time) [92]. A useful way to gain insight about this is to ask a person with diabetes 'What aspects of life are important for your quality of life?' and then 'How does your diabetes affect these?' [93].

Generic, health-related quality of life

Most attempts to assess quality of life actually assess health status, or what is commonly (and perhaps confusingly) referred to as *health-related quality of life*, with the two most frequently used measures being the Medical Outcomes Study Short-form 36 (SF-36) and the EuroQol EQ-5D [92]. In people with diabetes, such measures are typically more sensitive to differences between those with and without macrovascular complications or other non-diabetes-related comorbidities [94], or following major procedures such as pancreas transplant [95], than to differences between those with and without microvascular complications or using intensive versus conventional treatment regimens [96]. Large-scale studies comparing the health-related quality of life of people with various chronic conditions have typically found little evidence that it is differentially disrupted in adults with diabetes. For example, when

health-related quality of life was assessed in a large cohort of adults with diabetes using the Medical Outcome Study (MOS-36) questionnaire, people with diabetes reported more problems in physical and social functioning than those without chronic conditions, but tended to function better than people with cardiovascular, pulmonary, or gastrointestinal disorders [97]. For individuals with type 1 diabetes, poorer health-related quality of life is associated with being older, having biomedical complications, being female, being less physically active, and having a lower income [98]. Similarly, among individuals with type 2 diabetes, impaired health-related quality of life was associated with being female, the presence of diabetes-related complications, other non-diabetes-related comorbidities, and duration of diabetes [99].

Nieuwesteeg et al. [100] reviewed 17 studies that compared generic quality of life of children and adolescents with type 1 diabetes with that of their healthy peers. The authors concluded that the weighted effect sizes across all studies indicated no substantial differences in quality-of-life domains between children and adolescents with type 1 diabetes and healthy controls. On the other hand, disease-specific problems were certainly present.

Diabetes-specific quality of life

Diabetes-specific quality-of-life instruments do not enable comparisons between conditions, but they are more likely to be sensitive in measuring the impact of diabetes, and are also more responsive in assessing the consequences of treatment changes than generic or health-related measures [92, 93]. This is because they include domains that are particularly relevant to diabetes, for example dietary freedom, and exclude other domains of less relevance, such as mobility.

The Diabetes Quality of Life (DQOL) measure was the first questionnaire to be developed specifically to assess the impact of diabetes on quality of life [101]. It was designed for use in the DCCT to examine explicitly factors such as satisfaction, impact of diabetes, social and vocational worry, and diabetes-related worry. The DCCT findings suggested that quality of life is unimpaired by type of treatment (conventional or intensive insulin therapy) [102]. The apparently benign experience of being in the intensive-treatment arm of the DCCT (despite more injections, more blood glucose monitoring, and a threefold increase in severe hypoglycaemia) may be a consequence of the greater level of psychological and medical support provided in such clinical trials. Alternately, it may reflect the relative insensitivity of the DQOL measure, which is capable of detecting the impact of major treatments (e.g. pancreatic transplantation) but is less sensitive to the more subtle differences between types of insulin regimen [92, 93].

Another widely used tool to assess diabetes-specific quality of life is the Audit of Diabetes Dependent Quality of Life (ADDQoL) [103]. While healthy adults with type 1 diabetes or type 2 diabetes typically report a good overall present quality of life, they also indicate that the impact of diabetes on their quality of life is negative [103, 104]. In particular, the aspect of life most negatively impaired by diabetes is 'the freedom to eat as I wish', an item that captures eating what, when, how much, or how little the person prefers and, importantly, not having to eat when they do not wish to do so [104, 105]. Diabetes-specific quality of life is typically more negatively impaired for those using insulin compared with other medications, and for those living with one or more long-term complications [103]. However, several randomized trials demonstrate that more flexible and convenient treatment regimens (even when insulin is required) improve diabetes-specific quality of life compared with treatment regimens that impose more rigidity in terms of timing of medications and meals [105, 106].

The DAWN2 study shed light on the impact of diabetes on quality of life of 1368 adults with type 1 diabetes and 7228 adults with type 2 diabetes from 17 countries [61]. Overall, the impact of diabetes on various dimensions of quality of life was negative, with only 28% reporting a positive impact on at least one of the six life dimensions. A negative impact of diabetes on physical health was reported by 62% of respondents, followed by emotional well-being (by 46%), financial situation (by 44%), leisure activities (by 38%), work or studies (by 35%), and relationships with family and friends (by 21%). Around 40% of respondents reported that their medication routine interferes with their ability to live a normal life [61]. The measure used in the DAWN2 study (the DAWN Impact of Diabetes Profile) has since been validated, and is a brief, reliable, valid, and highly acceptable measure of the impact of type 1 diabetes and type 2 diabetes on quality of life [107]. It was also rated favourably in a study comparing five diabetes-specific measures of quality of life completed by adults with type 1 diabetes in the UK and Australia [108].

De Wit et al. have reviewed the instruments used to assess quality of life in young people with diabetes, identifying five diabetes-specific instruments, each with limited evidence regarding psychometric properties and various issues limiting their application in clinical practice [109]. The Pediatric Quality of Life Inventory (PedsQL) and the KINDL-R appear to be the most suitable instruments, but further research is needed to seek standardization of measurement in adolescents and to establish cross-cultural validity. Boys with type 1 diabetes report better diabetes-specific quality of life than the girls with type 1 diabetes [100]. More recent studies evaluating changes in quality of life associated with the use of continuous subcutaneous insulin infusion (CSII) have been mixed, with some indicating no benefit, while others suggested modest benefit [110], particularly among children and their parents [111]. Optimal metabolic management has sometimes [112], but not invariably [113], been found to be associated with better diabetes-specific quality of life in adolescents.

Age at onset of diabetes may also affect certain aspects of life quality. An early survey found that adults diagnosed with type 1 diabetes before 9 years of age were more satisfied with their marriage, and were more likely to have children than those diagnosed later [114]. The authors suggest that individuals diagnosed earlier in development may be more adept at integrating the condition as part of their lifestyle, and thus find less disruption from diabetes later in life. More recent work also suggests that the linkages between marital satisfaction, higher levels of diabetes-related satisfaction, and better glycaemic levels may reflect better psychosocial adaptation to a variety of illness-related and marital role stresses and strains [115]. Among older adults (mean age 81 years), the aspects of life most negatively impaired by diabetes are independence and dietary freedom [116].

Impact of psychosocial factors on diabetes self-management

The relentlessness of self-care, lack of immediate reward, unpredictability of blood glucose levels, and the feelings of guilt, anxiety, and failure that a person can experience when blood glucose levels are suboptimal (or unexplainable) can cause diabetes-specific distress, and may adversely affect general mood and

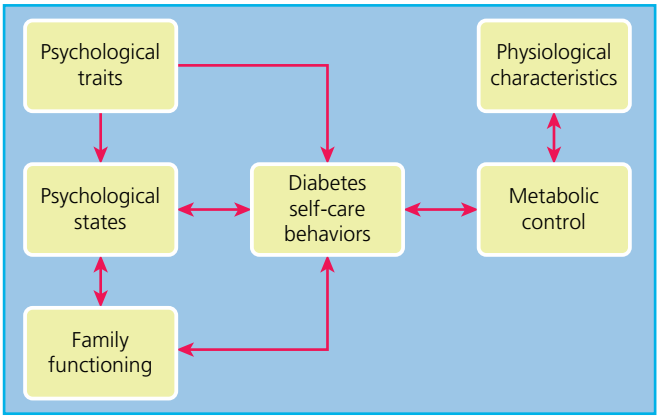

Figure 63.1 A systems model of the relationships between psychological, social, behavioural, and glycaemic factors.

emotional well-being. Conversely, certain personality traits or coping styles that are intrinsic to an individual's psychological make-up may modulate the person's ability to manage diabetes self-care activities, as may environmental and psychosocial factors, such as peer pressure to engage in certain 'forbidden' activities, disruptive interpersonal conflicts, and the normal stresses and strains of everyday life. Overall, an individual's *psychology* may influence, and be influenced by, the process of diabetes management.

According to a systems model of health, there is no simple direct relationship between any single psychological variable and glycaemia [117]. Rather, health outcomes are determined by a system of reciprocal relationships among multiple psychological, behavioural, and physiological variables. Figure 63.1 shows one such model of this process. Psychological *traits* are relatively enduring characteristics that include personality, temperament, and coping style. These may have an indirect impact on glycaemic levels, via their impact on self-care behaviours and emotional state. Psychological *states*, such as stress, are more transitory, reflecting emotions at a given point in time. These may influence glycaemic levels directly via the autonomic nervous system, or indirectly by affecting the individual's self-care behaviours. Both family interactions and self-care behaviours may affect, and be affected by, the individual's mood or level of stress. Family functioning, including conflicts and degree of family cohesiveness, can affect psychological state (and vice versa), but can also influence self-care behaviours. Self-care behaviours include medication use, diet, exercise, and monitoring, and these behaviours serve as the primary final common pathway to glycaemic levels.

Psychological traits and glycaemic state

Early psychological research in diabetes focused on the influence of personality traits, and found that glycaemia is more likely to be optimal in individuals with certain personality characteristics such as a strong need for achievement and a high level of responsivity to social demands [118]. By contrast, glycaemia tends to be worse in those who are opportunistic and alienated [119], or who have poor impulse control, a propensity for self-destructive behaviours, and difficulty maintaining interpersonal relationships [120]. A systematic review described that, in addition to genetic factors, several psychological constructs such as depression, lethargy, distress, disordered eating, anxiety, and family conflict were associated with higher HbA_{1c} in people with type 1 diabetes [121]. In adults with type 2 diabetes, higher neuroticism levels are associated with better glycaemic levels, suggesting that moderate levels of worry may be needed to motivate these older adults to manage their diabetes [122]. Furthermore, adults with type 2 diabetes and type D personality, defined as high negative affect coupled with high social inhibition, report more barriers to medication use and are less likely to eat healthily or to consult health professionals when problems with diabetes management occur [123].

Coping styles, broadly categorized as emotion focused and problem focused [124], serve to modulate the individual's response to stressful situations. Emotion-focused or cognitive coping attempts to reduce threats from the environment by reinterpreting or reappraising the situation ('Stay calm, it really cannot hurt you'). Problem-focused coping, in contrast, seeks to change the environment and thereby eliminate the threat. Within each of these categories, specific behavioural strategies may be differentially effective. Some may actually exacerbate stress (e.g. emotion-arousing strategies that include anger, impatience, or anxiety), while others (e.g. stoicism) may reduce or *buffer* the effects of stress [125]. In adolescents with type 1 diabetes, an emotion-focused coping style (e.g. behavioural and mental disengagement; aggressive coping) is associated with suboptimal glycaemic levels and reduced diabetes-specific quality of life, whereas active coping strategies (directed at approaching and making a direct effort to change the situation causing psychological distress) are linked to better glycaemic levels [126]. A meta-analysis of 21 studies has shown that the use of approach coping is associated with both better overall psychological adjustment and with somewhat better glycaemia [127].

Two recent reviews indicate that positive psychological characteristics (e.g. optimism, self-efficacy, and resilience) from childhood through to adulthood are consistently associated with optimal glycaemic levels, fewer diabetes-related complications, and reduced mortality rates [128, 129]. The mechanisms mediating these associations may include behavioural factors (e.g. medication taking, healthy eating) as well as reduced inflammation, and improved neuroendocrine and autonomic functioning.

Psychological states and glycaemic state

Another psychological state worthy of consideration is emotional stress. Stress stimulates the release of several stress hormones to mobilize energy to enable the *fight-or-flight* response. However, in people with little or no endogenous insulin production, stress-induced increases in blood glucose cannot be metabolized properly. Thus, environmental stress and the individual's emotional reaction have impacts on glucose management. A review by Buchberger et al. demonstrated a positive relationship between anxiety and HbA_{1c} in adolescents with type 1 diabetes [130].

The complexities of demonstrating the relationship between stress and glycaemia are exacerbated by the many variables that influence the generalizability of findings [131, 132]. Studies have been conducted in children, adolescents, and adults with type 1 diabetes or type 2 diabetes. Stressful experiences have been documented in self-report studies using simple checklists, validated questionnaires, or in-depth interviews, or in experimental studies with exposure to an array of stressors (mathematical problems, video games). The duration of exposure may be influential and the major limitation of such studies is that they do not necessarily reflect real-life stressors. Real-world stress can be caused by trauma, threat, major life events (e.g. bereavement or losing a job), chronic stressors (e.g. long-term unemployment or carer responsibilities),

or other day-to-day *hassles* (e.g. work, finances, relationships, exams, noise, illness, surgery). Furthermore, individuals perceive stressors in different ways, either as negative (e.g. death, financial problems) or positive (e.g. birth of a child, marriage). Exactly how stress affects glycaemia remains controversial and few empirical studies have been conducted [131, 132]. A five-year prospective study of 132 adolescents, using longitudinal growth curve modelling, found that stressful life events (reported annually) predicted greater psychological distress, and suboptimal self-care and glycaemic levels [133]. The effect was stronger in older adolescents and that the effect of stress on glycaemia was likely mediated by self-care behaviours.

Family characteristics, interactions, and glycaemia

Diabetes can dramatically disrupt the entire family, particularly when the individual with diabetes is a child or adolescent [134]. Children, especially younger ones, are more likely to have optimal glycaemic levels when their parents take an active role in managing their diabetes, whereas for adolescents, shared management responsibilities with parents typically results in more favourable outcomes [135–137]. A systematic review showed that family conflict is associated with higher HbA_{1c} [138], while a higher level of social support from family and friends was predictive of better dietary self-care [139]. Conversely, suboptimal glycaemic levels in children and adolescents is predicted by higher maternal trait anxiety levels [140], lower parental intelligence [141], greater levels of family stress, more family conflict and less family cohesion [142], and sociodemographic variables (e.g. single-parent households) [143]. In adults with diabetes, better marital satisfaction is associated with better diabetes-related quality of life [115, 144] and less diabetes-specific distress [115].

The relationship between family characteristics and glycaemia in children is most likely mediated via a behavioural pathway whereby family conflicts disrupt planning and performance of diabetes management activities; this pattern has been supported by a large prospective study [142]. A web-based portal has been developed that supports parents of children with type 1 diabetes, with online parent–professional communication, peer support, and information about diabetes [145]. The intervention did not reduce parenting stress [145].

Impact of behaviour on diabetes management

Historically, the terms *concordance*, *adherence*, and *compliance* have been used interchangeably to refer to the extent to which an individual simply follows their diabetes management regimen or plan, so-called *doctor's orders*. This model is now referred to as the *acute care model*. In recent years there has been a shift from the acute care model to chronic care models, and in terminology from *adherence* to *engagement* in self-care [146]. Chronic care models acknowledge the following:

- Almost 100% of diabetes care is self-care by the person with diabetes; only a few hours per year are spent with health professionals.
- Diabetes self-care is behaviourally complex. It can be helpful for healthcare professionals to consider diabetes self-care (e.g. taking insulin or other medications, glucose monitoring, eating healthily, counting carbohydrates, and maintaining physical activity) as a series of balls that need to be juggled, while balancing on a beam that represents life and all its competing demands (e.g. work, family, social life). If, from time to time, one or more balls are dropped, it is not something to be criticized or viewed as a character flaw, but rather it is because juggling all day, every day is challenging, tedious, and ultimately exhausting.
- Clinicians can offer advice, but optimal outcomes are dependent on the person with diabetes being fully engaged in adopting and sustaining the self-care behaviours. Only the person themselves is in a position to know what self-care activities are appropriate, possible, and sustainable in their unique living situation [147].
- The degree to which one *follows* a diabetes regimen cannot be determined easily, because there is no standard against which the person's actual behaviour can be compared. For example:
  - Few clinicians provide a written management plan that specifies all aspects of diabetes care.
  - Recommendations often differ between clinicians, and the extent to which the clinician has communicated clearly in the consultation or the extent to which the person agrees with the regimen discussed is often unclear [148].
  - As it is the person with diabetes, and not the healthcare professional, who is responsible for nearly all diabetes care, increasingly these outdated terms (concordance, adherence, compliance) and gross oversimplifications of the realities of living with and managing diabetes are being replaced with the question of the extent to which a person with diabetes *engages* in various self-care behaviours [146].
- Not all self-care activities are equal in value in terms of their relative effectiveness for optimizing glycaemia. Furthermore, certain self-care behaviours are far more likely to be maintained than others:
  - The international DAWN2 study demonstrated that taking medications as recommended and having a healthy diet are more common than self-monitoring of blood glucose and physical activity, and that engagement in these activities varies across countries [61].
  - Specific self-care behaviours are sometimes [149], but not invariably [150], related to glycaemic outcomes.

Behavioural factors: self-monitoring of blood glucose

Self-monitoring of blood glucose ought to be a particularly salient self-care activity. A large medical registry study of 24 312 adults with diabetes found that those with type 1 diabetes who self-monitored ≥3 times daily subsequently had HbA_{1c} values that were 1% (11 mmol/mol) lower than those who monitored less frequently [151]. For adults with type 2 diabetes using oral medication or insulin, monitoring at least daily was associated with a statistically and clinically significant reduction in HbA_{1c} (0.6% [7 mmol/mol]) [151]. For adults with type 2 diabetes not using medications (for whom there was no clear recommendation regarding glucose monitoring frequency), there was a statistically significant HbA_{1c} reduction (0.4% [4 mmol/mol]) compared with those not monitoring at all [151].

Other studies have provided less positive results. For example, a clinical trial comparing continuous glucose monitoring (CGM) with blood glucose monitoring found a difference in HbA_{1c} (0.5% [6 mmol/mol]) at 26 weeks favouring CGM in adults aged 25 years or older, but no difference among those aged 15–24 years or 8–14 years [152]. Use of CGM averaging six or more days per week was 83% in the adult group, 30% in the young adult group, and 50% in the paediatric group. These data indicate that active use of the

CGM device is crucial in achieving improved glycaemia, and that further work is needed to determine barriers to effective use.

In adults with type 2 diabetes not using insulin, the value of blood glucose monitoring is more controversial. A systematic review and a meta-analysis concluded there is little clinical benefit from blood glucose monitoring in this group [153, 154]. However, these reviews combined studies with considerable variation in trial design and implementation of blood glucose monitoring (education, frequency, and follow-up action) and it is unsurprising that little benefit was found *on average* [153–156]. Simply monitoring blood glucose values, and not using that information to adjust insulin or oral medications frequently and systematically, has little meaningful impact on long-term glycaemia; however, the reviews also suggest that there is considerable benefit to be derived by individuals who are motivated to monitor [155, 156]. A more recent clinical trial in adults with non-insulin-treated type 2 diabetes demonstrated that a structured approach to monitoring (incorporating these steps) indicates that blood glucose monitoring offers both clinical benefits (i.e. reduced HbA_{1c}, particularly in those following the protocol as intended) [157] as well as improved emotional well-being and confidence in diabetes self-care [157, 158].

It is noteworthy that blood glucose monitoring has no dose–response and is not an active agent (i.e. the mere act of checking blood glucose levels cannot reduce HbA_{1c}). Indeed, while blood glucose monitoring is often considered as a single self-care activity among many others, it is actually just one aspect of a complex intervention with multiple facets, including the following:

- Agreement on glucose targets between the person and their health professional.
- Discussion of people's motivations and associated beliefs about the necessity of but also their concerns regarding blood glucose monitoring.
- Timing and frequency of blood glucose monitoring.
- A supportive health professional trained in interpretation of glucose monitoring patterns.
- Appropriate training and feedback for the person with type 2 diabetes.
- Collaborative review of glucose monitoring patterns to identify areas for improvement and what may have contributed to the readings.
- A plan for how to change diet, physical activity levels, or medication.
- Behavioural change: modifying diet, increasing physical activity, or changing medication regimen.

Methodological issues in self-care assessment

The generally weak relationship between self-care behaviours and glycaemia remains problematic for any model purporting to predict successful diabetes management. This could reflect the possibility that HbA_{1c} is not the most appropriate glycaemic measure, but it is more likely that the unexplained variance in glycaemia reflects unspecified physiological or situational characteristics, as well as the difficulties inherent in measuring various self-care behaviours [159]. A review of 23 studies found that better medication taking was associated with lower HbA_{1c}, and this was a stronger relationship when medication taking was characterized in terms of prescription refills (78%; 7 of 9 studies) than when self-report (subjective) measures were used [160]. As self-care is typically assessed by asking people to describe their behaviour, rather than by direct observation, it is possible that self-reports may exaggerate or otherwise misrepresent the extent to which the person with diabetes performed a particular self-care behaviour [159]. Furthermore, self-care questionnaires typically ask the person to report on their average behaviour over the past week (or few weeks), whereas HbA_{1c} reflects average blood glucose over the past 8–12 weeks. Thus, *average* behaviours may be too crude and the two time periods are likely incompatible with a strong relationship. Finally, other factors such as stress, dietary behaviours, physical activity levels, hormonal changes, and other medications can affect blood glucose such that they may have an (unmeasured) influence on HbA_{1c}.

Interventions to reduce psychological distress and improve self-management, glycaemic outcomes, and quality of life

Reducing depression and diabetes distress

The treatment of depression among people with diabetes is both necessary and effective. A systematic review and meta-analysis of 14 RCTs involving 1724 adults with type 1 diabetes or type 2 diabetes demonstrated that treatment (psychotherapy, pharmacotherapy, or collaborative care) is effective in reducing depressive symptoms [161]; of the various treatment options available, the effect was greatest for psychotherapeutic interventions (Cohen's d –0.58). CBT appears to be particularly promising in reducing the severity of depressive symptomatology. CBT trains individuals to use problem-solving strategies to reduce stressful situations and to use cognitive techniques to *think away* their distorted beliefs, and replace them with more accurate and adaptive thoughts. Van Bastelaar et al. tested a web-based, diabetes-specific treatment of depression that was based on the principles of CBT, showing that this intervention reduced both depression and diabetes-specific distress [162]. A meta-analytical review of 13 RCTs on the efficacy of eHealth interventions in supporting the psychological and physical well-being of adults with type 1 diabetes or type 2 diabetes showed benefits for HbA_{1c} and depressive symptoms, although the effect on HbA_{1c} was not maintained [163].

Another effective treatment approach is mindfulness-based cognitive therapy (MBCT). MBCT is an eight-week protocolized therapy programme that can be delivered in groups or individually. MBCT combines meditation exercises with elements of cognitive therapy. The main goal of this intervention is the cultivation of mindfulness, which is the self-regulation of one's attention focusing on direct experience, while adopting an open, curious, and accepting attitude towards these experiences, especially one's psychological processes, such as thoughts and feelings. A systematic review of nine RCTs concluded that mindfulness-based interventions are effective in reducing depression, anxiety, and HbA_{1c} in people with diabetes [164]. Few studies have focused specifically on reducing diabetes-specific distress, though many intervention trials have included diabetes distress as a secondary outcome [56]. A systematic review of 41 such trials involving 6650 adults with type 1 diabetes or type 2 diabetes demonstrated no overall effect of intervention on diabetes distress [165]. Where diabetes distress was reduced, this was most likely to occur when the intervention was psychoeducational in nature, involving at least six sessions, over at least three months' duration, and delivered by a generalist rather than a mental health professional [165]. Further intervention studies focused specifically on the reduction of diabetes-specific distress are needed.

Importantly, people with diabetes do not necessarily want more access to specialist mental health services, but rather they prefer to discuss the impact of diabetes on their emotional and mental health with their diabetes healthcare professionals [166, 167]. Thus, in recent years an evidence-based practical guide was developed in Australia to enable healthcare professionals to develop their skills and confidence to have such conversations [168]. Adaptations have been made freely available for UK and US health professionals by Diabetes UK and the American Diabetes Association [169, 170], and the diabetes distress chapter is available in Danish from the Steno Diabetes Center Copenhagen.

Empowerment-based approaches

The *empowerment* approach encourages clinicians to understand what living with diabetes is like from an individual's perspective and to enable people with diabetes to take personal responsibility for their health, making self-selected choices about self-management [147, 171]. Embracing empowerment requires a paradigm shift on the part of clinicians to a position where they acknowledge that the person with diabetes is in control of, responsible for, and ultimately lives with the consequences of their own diabetes care. Knowledge is the cornerstone of empowerment. Empowerment programmes also aim to improve the person's ability to identify and set realistic goals, apply problem-solving strategies to overcome barriers to those goals, develop more effective coping strategies in general, manage stress more effectively, increase social support, and improve self-motivation. Empowerment occurs when the healthcare professional's objective is to enable the person with diabetes to make autonomous, informed decisions, and when the person with diabetes is doing so [171].

The theoretical argument is compelling and a review of qualitative studies describes positive experiences in using the empowerment approach [172]. However, surprisingly few trials have been conducted. Results from an early RCT demonstrated that when following a six-week empowerment programme, adults with diabetes showed a significant decline in HbA_{1c} as well as an increased ability to set goals, manage stress, obtain external support, and make decisions about diabetes management [173]. The limitations of this study include the short-term follow-up (six weeks post-intervention) and small sample (n = 64), which was highly educated (77% college education, 84% diabetes education). Other trials of person-centred consultation approaches have had less positive outcomes overall. For example, in a randomized trial involving 250 adults with newly diagnosed type 2 diabetes, in which clinicians in the intervention arm received 1.5 days' theoretical and practical training in person-centred consulting skills, the intervention group reported significantly better communication with the doctor, greater treatment satisfaction, and better psychological well-being than the control group [174]. However, there was no impact on glycaemic levels and cardiovascular risk increased, prompting the authors to urge caution that 'Professionals committed to achieving the benefits of patient-centred consulting should take care not to lose focus on disease while paying attention to the unique experience of illness of each patient' [174].

However, there is growing evidence and recognition of the role that language plays in how people think and feel about their diabetes [175]. The words we use to describe diabetes, people with diabetes, and the way in which it is managed have the power to motivate, elevate, and support or, conversely, to upset, demotivate, and harm. It is incumbent on all of us, as healthcare professionals, researchers, or policy makers, to ensure our language is neutral, non-judgmental, fact based, and free from stigma. It is important to use respectful, inclusive language that is person centred and strengths based (i.e. focused on positive attributes and what a person can do, rather than what they cannot do or have not done). In the past decade, numerous diabetes associations, health organizations, and groups of people with diabetes around the world have published position statements to demonstrate that #LanguageMatters. These include statements from Diabetes Australia, the International Diabetes Federation, the American Diabetes Association and Association of Diabetes Care and Education Specialists, NHS England, and Diabetes Canada, as well as from France, Italy, India, and Brazil.

Structured training and educational approaches

The education of people with diabetes has evolved from didactic information-giving ('obedience training to follow dietary prescriptions' [176]) one to one or in large groups, to theoretically driven, evidence-based, structured training in small groups, in which people with diabetes are able to talk with diabetes educators (nurses/dieticians) and their peers about their diabetes and problems with self-care, and learn the knowledge and skills they need for a life with diabetes (Chapter 26). This approach began in Germany in the 1980s, with the structured diabetes teaching and treatment programme developed by Michael Berger and Ingrid Mühlhauser, where several trials demonstrated the effectiveness of flexible, intensive insulin therapy for improving glycaemia in people with type 1 diabetes without increasing severe hypoglycaemia [176] (unlike the intensive treatment approach adopted in the DCCT [41]). In the UK, this approach was adopted as the Dose Adjustment For Normal Eating (DAFNE) programme, where an RCT demonstrated for the first time the unique combination of benefits for both biomedical and psychological outcomes [105]. Several studies have demonstrated sustainability of outcomes over the long term [177] and successful implementation in the real world [178, 179], while qualitative research has highlighted where the programme can be improved [180], and this is now the focus of further research (DAFNE*plus*) in the UK. The DESMOND programme offers a range of structured training sessions for people with newly diagnosed or ongoing type 2 diabetes, with RCTs demonstrating greater improvements in weight loss, smoking cessation, and beliefs about illness, although no benefit for glycaemia up to 12 months after diagnosis [181]. Three years later HbA_{1c} had improved in both groups, but no differences were observed between those receiving DESMOND or control intervention in any biomedical or psychological outcomes [182]. Importantly, improvements in four out of five health beliefs were sustained [182], and these were predictive of psychological distress at three years, indicating the importance of early formative experiences around diagnosis, and in terms of education provision and health provider support [183].

Programs have also been developed that teach those using insulin to recognize and anticipate blood glucose fluctuations to enable them to prevent extreme high and low levels, and reduce their fear of hypoglycaemia. A review demonstrated that the benefits of the face-to-face Blood Glucose Awareness Training (BGAT) programme, developed in the USA, can be substantial. There was a 57–92% reduction in severe hypoglycaemic events, a 65–86% reduction in driving mishaps, a 10–51% improvement in hypoglycaemia awareness, and a 6–21% reduction in fear of hypoglycaemia [184]. Several studies have been limited by small sample sizes, and by a focus on skills acquisition (estimation of blood glucose) rather than clinically important outcomes, such as severe hypoglycaemia. The German

face-to-face programme HyPOS has also demonstrated improved awareness of hypoglycaemia and reduced frequency of severe hypoglycaemia in a fully powered RCT [185]. The results of a new trial where BGAT is compared to a new intervention that addresses cognitive barriers to hypoglycaemia avoidance were published in 2019 [186]. The study was conducted in adults with type 1 diabetes and problematic hypoglycaemia, and outcomes include severe hypoglycaemia rates, hypoglycaemia awareness status, overall diabetes management, and quality of life [186].

Technological approaches

Advanced technologies for insulin delivery (e.g. predictive low glucose suspend pumps) and real-time continuous glucose monitoring (RT-CGM) have improved dramatically in recent years, and have the potential to reduce HbA_{1c} and fear of hypoglycaemia, and to improve quality of life [187]. In the first large-scale trial of sensor-augmented pump therapy in 485 adults and children with type 1 diabetes, over a 12-month follow-up sensor-augmented pump therapy offered significant advantages in terms of reducing fear of hypoglycaemia in adults and parents of children, as well as improving treatment satisfaction in adults, children, and parents [188]. However, such devices are expensive and require uninterrupted use, which many users find too burdensome. A 12-month observational study of sensor-augmented pump therapy in 15 countries in Europe and Israel found that improvement in HbA_{1c} was associated with more frequent sensor use [189]; average sensor use over 12 months was 30% (range 0–94%) and sensor use decreased with time (37% over the first three months, 27% over the final three months). For those with recurrent severe hypoglycaemia and its debilitating impact on quality of life, the adoption of technology into everyday management seems an obvious option. However, a clinical trial demonstrated that insulin pumps and RT-CGM offered no added benefit over multiple daily injections and standard finger-prick blood glucose monitoring for reducing severe hypoglycaemia, time spent in hypoglycaemia, or fear of hypoglycaemia, with the insulin pumps offering an advantage in terms of greater treatment satisfaction [190].

Most recently, the impact of *closed-loop* (artificial pancreas) technology has been investigated overnight in the home setting. Semi-structured interviews with 15 adolescents with type 1 diabetes using the technology and 13 parents demonstrated several perceived benefits (e.g. reassurance/peace of mind, confidence, time off from diabetes demands, safety, and improved glycaemic control) as well as disadvantages (e.g. difficulties with calibration, alarms, and size of the devices, and mixed effects were found on fear of hypoglycaemia) [191]. Semi-structured interviews with 24 adults using the technology have demonstrated similar positive and negative themes [192]. Although diabetes technologies have advanced considerably in the past decades, routine psychosocial assessment has not kept up with these new technologies. Although there is evidence supporting the use of CSII and CGM and, to a lesser degree, automated insulin delivery in terms of psychosocial outcomes, little is known about the barriers and facilitating factors regarding diabetes technology uptake [193].

Cognitive behavioural approaches to improve outcomes

Several meta-analyses have reported that psychological or psychotherapeutical interventions have modest effects in reducing psychological distress and improving glycaemia [194–196]. Traditional individualized and group therapy provides emotional support for both children and adults with diabetes, and may be particularly beneficial for those who are confronting the development of complications. When a time-limited, problem-oriented individualized treatment was compared with standard insulin treatment counselling in adults with type 1 diabetes, those receiving psychotherapy showed greater reductions in both problem severity and HbA_{1c} [197].

Coping skills training programmes are effective in improving the diabetes management skills of adolescents treated with intensive insulin therapy [198]. Based on a cognitive behavioural skills-building model, coping skills training presents participants with a series of social situations that are particularly problematic for adolescents, and asks them to demonstrate how they would resolve that situation (e.g. manage food choices with friends). As implemented by Grey et al. [198], groups of two to three adolescents role-play each scenario with a highly trained group leader who provides correction and models appropriate coping behaviour. Six weekly sessions lasting 60–90 minutes followed by monthly visits are typical for a training programme. Over a 12-month follow-up period, adolescents randomized to coping skills training plus intensive diabetes management had significantly lower HbA_{1c} (7.5% vs 8.5% [58 vs 69 mmol/mol]) and reported better self-efficacy as well as less difficulty in coping with diabetes and less depression when compared with adolescents who received intensive diabetes management alone [136].

Peyrot and Rubin [199] discuss the utility of including both problem-focused and emotion-focused interventions as part of an integrated behaviour change support programme. According to their model, interventions must occur in a particular sequence of five steps:

1. Specify the person's problem.
2. Translate the person's intentions to change into concrete, attainable goals.
3. Collaborate with the person to identify barriers to reach those goals and formulate effective strategies.
4. Establish a *contract* with the person to meet, or approach, those goals.
5. Provide continuing support.

This framework makes much sense from a clinical perspective. The extent to which such an approach is successful in initiating lasting clinically significant changes in mood, behaviour, and glycaemic control is likely to be dependent on the problem, the person, and the relationship with health professionals, but it is certainly an approach worth evaluating in formal clinical trials. Arguably, this was the basis of the Comparison of Optimised MDI versus Pumps with or without Sensors in Severe Hypoglycaemia (HypoCOMPaSS) study, which demonstrated prevention of severe hypoglycaemia and reduced fear of hypoglycaemia in a six-month RCT [190]. A systematic review and meta-analysis of 12 RCTs concluded that CBT improved short- and medium-term HbA_{1c}, but no significant effect was found in the long term [200]. CBT also decreased anxiety and depression (short and medium term) and long-term depression, while conflicting results were reported for diabetes-specific distress and quality of life [200].

Psychotherapeutic and family-focused approaches

Several behavioural and psychological interventions have been developed to improve engagement in self-care among people with diabetes [199, 201]. These differ from more traditional group therapy programmes in so far as they use several sessions to target one or more self-care behaviours and the psychological factors that may

interfere with optimal self-care. A typical self-management programme may meet once or twice monthly for seven or more sessions, discuss specific self-care strategies (e.g. glucose monitoring, physical activity), role-play appropriate behaviours, use homework assignments to practise what has been learned, and resolve problems or barriers encountered during diabetes management. Variations on this basic theme include the use of 6- or 12-monthly *booster* sessions after the end of the programme, which are designed to review and reinforce previously learned material. Interventions developed initially for people without diabetes with high levels of psychological distress are increasingly being applied to persons with diabetes, and both CBT and *motivational interviewing* [202, 203] or *motivational enhancement therapy* [179] programmes have led to modest improvements in HbA_{1c} and in self-reported quality of life.

Family-focused behavioural interventions are particularly successful in improving diabetes management in children. In one of the largest studies of its kind, Wysocki et al. randomized 119 families of adolescents to either 10 sessions of behavioural family systems group therapy, 10 sessions of an education and support group, or standard diabetes therapy (with minimal psychological support) [204]. Behavioural family systems therapy included four modules:

- Problem-solving training, which focused on conflict resolution.
- Communication skills training.
- Cognitive restructuring to identify and change those attitudes and beliefs that impede effective communication.
- Specialized family therapy interventions.

In the 12 months following treatment, adolescents who participated in behavioural family systems therapy showed long-term improvement in relationships with their parents compared with adolescents in the other two treatment groups, and also manifested improved adherence to their diabetes management regimen, although these behavioural and psychological changes were not associated with improvements in metabolic control [205]. Similar interventional approaches have also been applied to older adults with type 2 diabetes and, as is the case with children and adults with type 1 diabetes, there are reductions in psychological distress and occasionally, but not invariably, small improvements in long-term glycaemia [206].

Conclusion

Diabetes is a behaviourally, psychologically, and cognitively demanding chronic condition. One of the greatest problems facing people with diabetes is the failure, or inability, of many clinicians to empathize with how challenging it is to live with the daily self-care demands of a condition like diabetes, to identify those experiencing psychological distress quickly, and to provide appropriate support. From this chapter, it is clear that people with diabetes have a remarkable level of psychological resilience but, like anyone else, they may experience psychological distress, made more likely by having to cope daily with the demands of living with a chronic condition. It is evident that the behavioural changes needed for optimal self-management are unlikely if the person lacks the prerequisite information, motivation, and/or behavioural skills. Furthermore, such changes are unsustainable if they cannot be incorporated into the person's lifestyle, if they compromise their quality of life, and/or if they are not supported by family/friends and healthcare professionals. It is incumbent on all members of the healthcare team to recognize the complex psychosocial impacts of diabetes and to continue to develop better ways of delivering healthcare and support in order to alleviate distress, improving both biomedical health outcomes and quality of life.

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64 Role of Cognitive Function in Managing People with Diabetes

Tamsin Santos, Chelsea Baird, Sally Eastwood, Kerrie Shiell, and Joseph E. Ibrahim

Queen Elizabeth Centre, Ballarat Health Service and Department of Forensic Medicine, Monash University, Melbourne, Australia

Key points

- Cognition refers to a range of mental processes or thinking skills, which help us to acquire knowledge and understanding through thought, experience, and sensation.
- Adults with type 1 diabetes may have impairments in multiple cognitive domains, including attention (visual and sustained), visual perception, processing speed, and executive function (concept formation, cognitive flexibility, and anticipation). The cognitive domain of memory as well as learning can be spared.
- Type 2 diabetes is associated with declines in the cognitive domains of executive function, processing speed, memory, and language (verbal fluency).
- Clinicians should screen older individuals with diabetes for cognitive impairment using a standardized test.
- A formal diagnosis of dementia is needed to develop a tailored management plan.
- It is important to consider and evaluate mood for comorbid depression.
- People with diabetes and declining cognitive function are at greater risk of both hyperglycaemia and hypoglycaemia due to difficulties with learning and retaining new knowledge and an inability to recognize the importance of self-care.
- The presence of dementia must be integrated into decisions and care planning; however, it should not detract from seeking to achieve optimal management.
- Re-evaluating glycaemic management plans should occur at least annually. This should be a comprehensive assessment, taking into account cognitive screening performance and lived experience.
- Polypharmacy is common in older adults and increases risks for drug interactions, medication errors and omissions, falls, and cognitive impairment. Medication management including regular review and appropriate de-prescribing is essential for optimal care in people as they grow older and have chronic disease and dementia.
- Social isolation is a risk factor for cognitive decline and dementia. Social support for individuals with diabetes and dementia is important. Education and support for carers are needed.

The role of cognition and the impact of cognitive impairment in sustaining self-care in people with diabetes are both under-recognised and underappreciated. Physicians often fail to identify cognitive impairment in as many as 56% of individuals [1]. As a result, these people do not receive adjustments in their treatment plan to compensate for their cognitive abilities. With an ageing society and the increasing prevalence of multimorbidity, it is crucial for clinicians to understand the nature and impact of cognitive impairment to manage their chronic health conditions successfully.

Type 1 diabetes accounts for about 5–10% of all people with diabetes [2] and although life expectancy is still shorter than those without diabetes, people with type 1 diabetes now live much longer than they did three decades ago. This prolonged lifespan puts them at risk of developing dementia [3]. The risk ratio for dementia in inpatients with type 1 diabetes is 1.65 times more than in people without diabetes [4] and people with type 2 diabetes are almost twice as likely to develop dementia [5].

This chapter begins by describing and defining cognition function, then addresses the nature of dementia and the associations between diabetes and dementia. The second half of the chapter presents four case studies to demonstrate the application of this new knowledge of theory and principles into clinical practice.

Cognition

To fully appreciate cognitive impairment in its many forms, the clinician must first develop an understanding of cognition.

Definition of cognition function

In broad terms, cognition refers to a range of mental processes or thinking skills, which help us to acquire knowledge and understanding through thought, experience, and sensation [6]. These skills have been characterized in various ways, but commonly fall into six cognitive processes or domains:

- Attention
- Processing speed
- Visual perception

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- Memory
- Language
- Executive function [7].

Attention involves the brain's ability to allocate cognitive resources to focus or switch one's focus between competing information or stimuli. Imagine the golfer who must ignore all extraneous distractions to successfully complete the putt. In contrast, *processing speed* relates to the time a person requires to understand and respond to information. Clinically, people with reduced processing speed take longer to formulate an answer and respond to questions. The next process, *visual perception*, involves our ability to interpret and understand stimuli in the real world and to understand the physical relationship between self and the environment. Examples include being able to correctly thread buttons through buttonholes, coordinate tools and utensils, and even find your way. *Memory* refers to the processes necessary for the acquisition, storage, retention, and retrieval of information for future use. This is a necessary precursor for successful self-care, as one needs to remember appointment times, manage medication, and track blood glucose levels.

In contrast, when examining *language*, the clinician will need to consider the person's ability to comprehend speech and express themselves through language. Disorders in this domain may be quite isolating for the individual, as they are unable to express their needs or understand instructions and information being conveyed by others. The final cognitive process, known as *executive function*, is an umbrella term used to describe a set of complex cognitive processes required for mental control and self-regulation of behaviour and emotion. These processes oversee and coordinate other aspects of our thinking, emotion, and behaviour. These include such things as planning, judgement, abstract reasoning, emotional regulation, self-monitoring, initiation, and inhibition. Impairments in these areas can have substantial implications for a person's ability to monitor their health and seek support when necessary. Executive dysfunction is often overlooked, and people with these deficits are commonly labelled as *non-compliant* and/or *difficult patients*.

Assessing and measuring cognitive function

Several widely available validated cognitive screens are commonly used to detect cognitive impairment. The standardized Mini Mental Status Examination (sMMSE) is a 30-item test, which assesses orientation, attention, language, memory, and perception in older adults. If an individual scores below 24 correct items on the test, this is usually considered indicative of cognitive impairment [8].

Unfortunately, the sMMSE does not formally assess executive function, which is a crucial cognitive domain for self-care in general and specifically for self-managing chronic disease such as diabetes. Another commonly utilized screen is the Montreal Cognitive Assessment (MoCA) [9]. This is also a 30-item measure, which is more sensitive to identifying cognitive impairment, and it assesses a broader range of cognitive processes, including executive function. Both measures are quick to administer and provide the clinician with some understanding of the person's cognition.

There are many other cognitive screening tools developed for specific populations or subgroups. For example, the Rowland Universal Dementia Assessment Scale (RUDAS), which was developed in Australia, is another routine cognitive screen designed for people from diverse cultural, educational, and linguistic backgrounds. This relatively brief screen assesses orientation, praxis, judgement, language, and memory, which enables the clinician to develop an understanding of cognition, while controlling for a range of demographic variables that could otherwise deflate the performance.

Assessing cognitive function using these standardized tests provides an indication of the severity and extent of the individual's cognitive function. It is important to remember that the tests are not a diagnostic tool for any specific neurocognitive condition, but act as a screening facility.

Comprehensive neuropsychological assessment remains the gold standard and requires an in-depth examination of the six cognitive processes already described, together with a consideration of the impact of mood and behaviour. These investigations are combined with observations from the clinician, the clinical history, and reports from significant others to ensure that the psychometric data is understood in context.

These rigorous clinical assessments along with laboratory and neuro-imaging studies are used to formulate a diagnosis of the underlying cause of a person's cognitive impairment.

Cognitive impairment and dementia

Cognitive impairment is diagnosed when an individual's performance, on at least one of the domains, is significantly below their premorbid level of function. An understanding of premorbid function is commonly derived through discussions with the individual or family about levels of occupational and educational attainment, or via measures resistant to the effects of brain insult [10].

Cognitive impairment may be associated with a range of congenital or developmental conditions. However, in later life, cognitive impairment is often associated with a traumatic event or disease process affecting normal brain function.

Dementia is one of the most common conditions influencing cognitive function in older people [11]. Dementia itself is an umbrella term, used to describe a range of devastating, pervasive, neurodegenerative processes, which progressively render a person uncommunicative, bed-bound, and fully dependent on others for all personal care. In the most recent revision of the Diagnostic and Statistical Manual (DSM-5) [12], dementia has been termed *major neurocognitive disorder*. By definition, a major neurocognitive disorder is diagnosed when there is significant change in at least one cognitive domain, coupled with significant deterioration in the individual's ability to independently manage activities of daily living. These changes are not primarily attributed to another mental disorder, nor do they occur exclusively in the context of a delirium [7]. A minor neurodegenerative condition (or mild cognitive impairment) is diagnosed when the extent of cognitive and/or functional impairment is comparatively modest.

These illnesses are caused by pathological changes to the brain. Each condition is differentiated by the type and location of its pathology, and the resulting changes to thinking skills, personality, and behaviour. For example, abnormal protein deposits in the medial temporal lobe are widely believed to explain the memory dysfunction seen in Alzheimer's disease.

The World Health Organization (WHO) estimates that around 50 million people are currently living with dementia, with rates expected to rise to 82 million by 2030, and 152 million by 2050 [11].

Dementia and diabetes

Impact of dementia as a comorbidity in a person with diabetes

Suboptimal self-care in people with diabetes and cognitive impairment or dementia increase the risk of poor clinical outcomes, with

higher frequencies of hyperglycaemia, hypoglycaemia, and diabetes-related complications [13].

The presence of cognitive impairment or other comorbidities may inappropriately influence management plans, leading to setting or accepting more lenient glycated haemoglobin (HbA_{1c}) targets, as well as fewer investigations and reduced engagement with specialist services [14]. In addition to chronic hyperglycaemia (HbA_{1c}>9% [75 mmol/mol]), hypoglycaemic episodes are also more prevalent in those with cognitive impairment or dementia. Subsequently, these episodes may worsen a person's cognition, impair performance on the sMMSE, and reduce medication taking and self-care in this cohort [15].

With the rise in prevalence of both dementia and diabetes worldwide, it is important for healthcare professionals to be aware of the coexistence of these conditions in individuals with diabetes to understand how these cognitive changes affect management [16]. Additionally, identifying which cognitive and self-management domain(s) is/are impaired in a person with diabetes allows clinicians to implement self-care strategies better suited to the strengths of the individual [16, 17]. Optimizing an individual's self-care functions enhances glycaemic management and possibly prevents or slows the progression of the multitude of damaging diabetes-related complications.

Differences in cognitive function between type 1 diabetes and type 2 diabetes

Both type 1 diabetes and type 2 diabetes have been associated with the development of dementia [18]. Adults with type 1 diabetes can have impairments in multiple cognitive domains, including attention (visual and sustained), visual perception, processing speed [19], and executive function (concept formation, cognitive flexibility, and anticipation) [20]. The cognitive domain of memory as well as learning can be spared [19]. Acute hyperglycaemia (>15 mmol/l; 270 mg/dL) in adults with type 1 diabetes affects performance on psychomotor tasks and mental subtraction speed, as well as increasing subtraction errors in the processing speed cognitive domain [21]. Acute hypoglycaemia impairs the cognitive domains of visual perception (spatial ability) [22], attention (flexibility), and processing speed [23].

In type 2 diabetes, many longitudinal studies suggest an association with declines in the cognitive domains of executive function, processing speed, memory [24], and language (verbal fluency) [25].

Pathogenic mechanisms linking diabetes with dementia

Type 1 diabetes

The mechanisms underlying cognitive impairment in type 1 diabetes are complex. These can be influenced by the age of onset of diabetes, duration of diabetes, occurrence and severity of hypoglycaemia and hyperglycaemia, presence of cerebral white-matter changes, cerebral atrophy, and vascular disease. The discussed mechanisms can lead to the development and progression of both vascular and Alzheimer's dementia subtypes [26]. We explore three of these variables in more detail.

Onset of diabetes

Early-onset type 1 diabetes – that is, in children younger than 7 years of age – is an important factor influencing cognitive function in adulthood, as the younger developing brain may be more vulnerable to the effects of hypo- and hyperglycaemia [27].

Disease duration

Disease duration in adults with type 1 diabetes is inversely associated with cognitive performance and is a strong predictor for impaired cognitive function in memory (delayed recall) [28], psychomotor speed [29], processing speed, attention, language (verbal ability), and executive function [30].

Hyperglycaemia

The incidence of cognitive impairment in people with diabetes and chronic hyperglycaemia is 28% compared to 5% in the general population [31]. Chronic hyperglycaemia may trigger mechanisms that promote neuronal damage and endothelial dysfunction, resulting in the development of cognitive impairment over time [32]. Furthermore, chronic hyperglycaemia dramatically increases the risk of microvascular disease typically attributed to diabetes (retinopathy, nephropathy, and neuropathy), which is also associated with cognitive impairment [26].

Type 2 diabetes

Type 2 diabetes is associated with lower total brain volume [33], grey–white-matter volume, more cerebral infarcts, and white-matter hyperintensity volume, which all mediate cognitive impairment [34]. Type 2 diabetes, particularly when treated with insulin, is associated with both vascular and Alzheimer's dementia [35].

Although the association with vascular and Alzheimer's dementia is not only explained by an increased prevalence of clinical strokes, it also remains possible that silent infarctions are due to type 2 diabetes pathology [35]. Furthermore, in the subgroup of people with type 2 diabetes treated with insulin, the association with both dementia subtypes is independent of education level, smoking, body mass index, presence of atherosclerosis, systolic blood pressure, and antihypertensive medication use [35].

Vascular dementia and type 2 diabetes

Like cerebrovascular events (also referred to as *stroke*), risks factors for vascular dementia include hypertension, diabetes, advanced age, male sex, smoking, and cardiac diseases [36].

Alzheimer's dementia and diabetes

The correlation between type 2 diabetes and Alzheimer's dementia is strongest in people treated with insulin. This may represent more serious and long-standing diabetes, but also that exogenous insulin itself or hypoglycaemic episodes (which frequently complicate insulin therapy [37]) increase the risk of Alzheimer's dementia. A direct correlation has been reported between increased endogenous insulin levels and impaired cognitive function [38].

The common finding of cerebral infarctions and subcortical white-matter lesions in Alzheimer's dementia suggests that underlying vascular factors may also be important in late-onset Alzheimer's dementia [36]. Some studies suggest that in addition to vascular disease, alterations in glucose, insulin, and amyloid metabolism underlie the pathophysiology of Alzheimer's dementia [18].

Some other mechanisms such as glycation of proteins and advanced glycation end-products may also be involved in the aetiology of diabetes complications, as these can be found in the plaques and tangles of individuals with Alzheimer's dementia [39]. Advanced glycation end-product epitopes have even been detected in the earliest states of Alzheimer brain lesions and promote known plaque and tangle properties. Progressive glycation augments the deposition of proteins by crosslinking, and it induces macrophages to secrete acute-phase reactants, thereby stimulating an

immune-cell response, possibly contributing to nerve-cell death by the formation of free radicals [40].

Type 2 diabetes also directly affects neurotransmitter metabolism, which can contribute to Alzheimer's dementia. Decline in blood–brain barrier transport of choline (precursor of acetylcholine) [41], decreased acetylcholine synthesis by brain glucose utilization/insulin-induced hypoglycaemic episodes, blockade of acetylcholine muscarinic receptors, and loss of cholinergic activity can all disrupt higher cognitive functions and affect the severity of Alzheimer's dementia [42].

Clinical management of people with cognitive impairment and diabetes

Self-management

Optimal management of chronic disease such as diabetes requires effective self-management to maintain independence [43] and reduce morbidity and mortality [44]. As self-management is a strong predictor of morbidity, a better understanding of how to improve cognitive, emotional, and physical abilities to manage disease is essential [45]. Self-management improves glycaemic levels [46] and can reduce mortality by a hazard ratio of 2.21 [47]. The five domains of self-management (Box 64.1) are:

- Problem solving.
- Decision making.
- Finding and utilizing appropriate services.
- Working with healthcare professionals to make decisions about treatment.
- Taking action [17].

Some key self-management behaviours in diabetes include following complex medication regimens (applying to both oral and injectable drugs), appropriate timing of insulin doses, performing and interpreting blood glucose testing, healthy eating plans, adequate exercise, satisfactory foot care, and attending screening examinations and tests for potential end-organ complications [48].

Self-management and dementia

Self-management is particularly challenging in older people with diabetes and comorbid cognitive impairment [14]. The impact of dementia on a person's ability to self-manage their diabetes depends on which cognitive domain(s) are affected, the severity of impairment in the domain(s), and then the complexity of the required self-management tasks [17].

It is crucial for clinicians to recognize and assess older people with cognitive impairment and then consider the impact this impairment may have on self-management domains (Box 64.1) [16, 17]. This knowledge will assist clinicians in developing management plans tailored to the individual and work to circumvent any barriers imposed by the cognitive impairment.

Individuals with diabetes and cognitive deficits associated with dementia may experience impairments in all the domains relevant for successful chronic disease self-care [16]. An abnormal sMMSE

Box 64.1 Self-care domains, tasks involved, and implicated cognitive domains

Self-care of the individual		Cognitive domain implicated	Impact of impairment, possible presentations
Problem solving: identifying problems and generating solutions	Acquiring information	A, LM	Repetitive questioning or disengagement; unable to recall information; rapid forgetting
	Understanding information	E	Unable to acknowledge extent of health issues; dismissive of solutions
	Generating solutions	E	Unable to generate simple solutions
Decision making: acting in response to changes in disease condition	Appropriate solution choice	E, LM	Concrete responses; poor understanding of management
Finding and utilizing appropriate resources	Medical device use	P, V, La	Failure to take medication and follow lifestyle regimen
	Attending clinical appointments	E, V	Failure to attend appointments; gets lost; unable to access transport
Working with healthcare professionals to make decisions about treatment	Negotiating goals of care	E	Unable to agree on goals of care and may appear stubborn
	Communicating with services and others	La	Unable to describe symptoms; delay in seeking help; argumentative
	Psychological and emotional adjustment	E	Overwhelmed at changes in care regimen; frustration or aggression
Taking action	Monitoring, medication taking, and lifestyle change	E, LM, Mo	Impulsivity; unable to override ingrained behaviour patterns; poor medication taking; low mood

A, attention and information processing; E, executive function; La, language; LM, learning and memory; Mo, mood and motivation; P, praxis; V, visuospatial and constructional.
Source: Modified from Ibrahim et al. 2017 [17].

score (<24) corresponds with decreased self-care, diabetes monitoring, independence in activities of daily living, and a need for increased personal care assistance and more hospitalizations [14].

Collaborative approach

Clinicians should work in collaboration with people with diabetes and caregivers to assess an individual's current capabilities, identify potential barriers to successful self-management, and make efforts to adjust the provision of information according to the person's skill set [17].

Cautionary tales

Mistaken assumption of clinical futility

Often a pre-existing diagnosis of dementia may take precedence in the clinical approach to managing a person with diabetes. When this occurs, treatment options may be discounted based on a misguided notion that there is global cognitive impairment. This potentially leads to suboptimal treatment and avoidable morbidity and mortality [49].

Life expectancy for people with Alzheimer's dementia may range from 3 to 10 years, largely dependent on the initial age of diagnosis [50]. However, from the initial cognitive symptoms, life expectancy may be as long as 20 years [51], a significant period over which to limit complications of diabetes and empower the self-management abilities of the individual.

Misattribution of 'failures in adherence'

Labelling individuals as resistive and deliberately non-compliant may also occur as a person's cognitive decline progresses. As cognitive function becomes more impaired, individuals may be unable to take appropriate action to prevent or treat hypoglycaemic episodes [14, 52].

Clinicians may mistakenly assume that the individual is disinterested, unmotivated, or even recalcitrant. However, hypoglycaemia in the setting of pre-existing dementia could be secondary to a poor response to the prescribed regimens [15], along with a reduced understanding of diabetes management [52].

Carer involvement

Educating carers about diabetes management is important. It is also beneficial for self-care tasks to be bolstered by social supports, even though this may not necessarily improve glycaemic levels (HbA_{1c}) [52].

Balancing improvements in self-management tasks versus glycaemic levels is important for people with dementia as tight glycaemic targets may have their own disadvantages, such as falls, in this vulnerable population. Hypoglycaemia may result from poor cognition [13] as well as setting overly intensive glycaemic targets [53].

Targeted management plans

Developing targeted management plans requires clinicians to consider the variability in severity and types of cognitive impairment. Healthcare professionals must challenge the assumptions that cognitive impairments in dementia are global and similar between individuals, and refute that treating people with dementia is futile [16].

Glycaemic targets in individuals with diabetes and comorbid dementia must be correlated with a person's level of cognitive impairment, cognitive domains affected, underlying prognosis, likelihood of distressing symptoms, and the person's health and lifestyle wishes. There are numerous suggested guidelines from medical and clinical experts around the world and these are notable, as they highlight the importance of tailoring treatment for each individual [54].

Tailored management plans should focus on the individual's diabetes management knowledge, motivation, perceptual problems, and effects of the condition on eating and drinking appropriately [55]. To add to this complexity, clinicians must also understand how cognitive processes and self-management challenges vary depending on the nature and severity of the person's comorbid neurodegenerative process.

Depending on the dementia subtype, any of the cognitive domains (attention and information processing, language, visuospatial ability and praxis, learning and memory, and executive function) may be impaired. Impairment in one or more of these cognitive domains can affect the five key processes of chronic disease self-management [17] (Box 64.1).

Case studies

This section provides four case studies demonstrating different presentations and aspects of clinical management.

Case Study 64.1 Mild cognitive impairment and delirium

Mrs A was a 91-year-old female retired school teacher, who lived alone and was proud of self-managing type 2 diabetes. She was treated at an acute hospital following a fall and fractured hip, complicated by a urinary tract infection and hyperglycaemia. Two weeks after returning home, Mrs A became unwell and appeared more confused when family members spoke with her. A visit to the emergency department revealed the presence of hyperglycaemia, hyperosmolar non-ketotic coma, a urinary tract infection, and rapid atrial fibrillation.

The case study 64.1 of Mrs A highlights the importance of recognizing the impact of both immediate and longer-term impairments on a person's ability to manage their own healthcare needs. People with diabetes must have a certain level of both physical and cognitive prowess to monitor and maintain blood glucose levels and adapt treatment regimens. Unfortunately, Mrs A's medical history (age, living alone, diabetes, urinary tract infection, pain from fracture, and surgery) not only makes her more susceptible to delirium, but also puts her at greater risk for developing a major neurocognitive disorder.

Short-term impairment: delirium

Acute changes in cognition are often accompanied by associated changes in function. For Mrs A, the confusion resulting from her delirium would compromise her ability to monitor her blood glucose levels and make the necessary adaptations to her treatment regimen.

The presence of infection and reduced mobility significantly increases her risk of delirium [56], a serious condition that can lead to persistent cognitive changes, functional decline, and premature institutionalization [57]. This acute medical condition affects a person's ability to maintain their attention and level of awareness.

It develops quickly, usually within hours to days, and may present with cognitive fluctuations in memory, orientation, language function, or perception [12]. While the condition often resolves over time, many people still experience a degree of permanent cognitive impairment or a sudden worsening of subtle pre-existing deficits.

Long-term impairment: dementia

In Mrs A's case, her increasing age and the presence of type 2 diabetes heighten her risk of both Alzheimer's disease and vascular dementia. However, the implications for Mrs A are substantial, with changes commonly seen in memory, attention, and executive dysfunction in vascular dementia, and additional perceptual and language changes in Alzheimer's disease [7]. These cognitive deficits will compromise Mrs A's ability to manage her chronic health condition.

Mrs A would need reasonable *attention* to sustain her focus while discussing her treatment regimen with health practitioners. Attention is a necessary first step for all cognitive processes. Without attention, Mrs A would be unable to register or retain information about changes in her treatment or learn to utilize treatment aids.

Similarly, impaired *processing speed* may have a significant impact, particularly in circumstances where Mrs A is receiving lengthy verbal descriptions about changes in treatment. A person with slowed processing will struggle to integrate this information.

The implications of cognitive impairment are often under-recognised and frequently underappreciated. Consider the impact of *language* or *visual perceptual* deficits in Mrs A's case, with poor perceptual abilities hampering her ability to manipulate the equipment necessary to monitor and treat her diabetes. If her language is compromised, she will struggle to comprehend changes in her treatment plan, or express concerns about her care.

All too often, the orthopaedic injury becomes the focus of care, with little consideration given to the interplay of risk factors affecting short- and long-term cognitive impairments and how these impairments influence the person's health outcomes.

Key learning points

Mrs A's acute orthopaedic hospitalization represents a good opportunity to review her cognition, diabetes care, and self-management abilities. During the hospital admission, every opportunity should be utilized to assess a person's cognition and function. This includes formal testing as well as questions and observations required as part of the care of the individual. For example, when considering memory:

- Can Mrs A recall her postoperative instructions for hip precautions?
- Does her level of recall match her actions?
- Does she appear to remember you on successive visits?

When considering processing speed:

- Is there a considerable delay in the speed of her response to questions?
- Does she appear confused by lengthy instructions?

When considering attention:

- Does she maintain eye contact with you during conversation?
- Is she distracted by extraneous noise and people walking by?

Delirium is very common in hospitalized individuals. Delirium is an acute alteration in attention and cognition. It is a medical emergency and may be the initial presenting symptom for a myriad of medical problems, prompting a search for the underlying precipitant.

Home assessments may assist the team with discharge planning to ensure that the home environment is well set up for Mrs A's needs and to further review her cognition within her home environment. Cognitive function needs to be reassessed once the delirium has resolved; this may take several weeks or months.

Case Study 64.2 Multidisciplinary management of diabetes and dementia

Mrs B was a 75-year-old woman who lived at home with her husband. Past medical history included being a cigarette smoker with chronic obstructive pulmonary disease (COPD), dementia, type 2 diabetes, depression, osteoarthritis, and oesophageal ulceration.

Mrs B had a fall, sustaining a fracture of the left ankle, and remained in hospital for almost nine weeks. Mrs B's mobility had declined and she was no longer able to ambulate independently. Her unstable diabetes could only be managed with the introduction of twice-daily insulin to her medication regimen. Her husband (and carer) was worried about administering insulin. Despite this, Mrs B and her husband wished to return home. Hospital staff were concerned that Mrs B's care needs were now too high to be met in the community.

A medical assessment determined that Mrs B lacked the capacity for decision making. This led to an application being filed for a guardian to make medical, accommodation, and lifestyle decisions. An independent guardian was appointed for 12 months. Following an investigation, the guardian supported Mrs B and her husband's decision to return home.

After returning home, Mrs B's diabetes management was coordinated through her usual local medical officer and visiting community nurses. However, Mrs B's husband found it increasingly difficult to access the community and their visits to their local general practitioner became less frequent. Mr B then cancelled community nursing visits, citing that Mrs B no longer wanted to continue to engage with the service and that he would continue to manage his wife's diabetes.

One afternoon, Mr B called an ambulance as he found his wife unresponsive in her armchair. On arrival, Mrs B's blood glucose level was 2.6 mmol/l. She was transported to the emergency department where she was found to have aspiration pneumonia.

The case study 64.2 of Mrs B highlights the complexities that arise from ageing, disability, dementia, multiple comorbidities, and psychosocial circumstances.

The context of care and understanding the other health professionals who can contribute is important information for medical practitioners providing care to people with diabetes. While the expectation is that a medical practitioner will focus their time and energy on clinical requirements, for example ensuring glycaemic levels, the role must be much greater.

Multidisciplinary team

The involvement of a multidisciplinary team is essential for the successful transition of a person with diabetes and cognitive impairment from hospital to community-based care. Ideally, a multidisciplinary team assessment would enhance the person's independence and promote interventions for sustainable management in the community.

When a multidisciplinary team assesses and provides intervention to individuals with diabetes, it provides a holistic approach to the care needs of the person. This approach is also driven by the primary aetiology and chronology of diagnoses:

- Does the person have pre-existing diabetes and has subsequently developed a cognitive impairment?
- Does the person have a pre-existing cognitive impairment and subsequently developed diabetes?

The answers to these questions will shape how the multidisciplinary team approaches the person's care needs and the interventions they will provide. If the person had pre-existing diabetes, then they may retain that pre-existing knowledge and embedded skills required for managing this condition. Any new changes to management may be difficult to retain and the person may revert to their previous well-established practice or habits. In the other situation, if a person has a pre-existing cognitive impairment, then acquiring any new knowledge and skills required to self-manage diabetes will be challenging for the individual with diabetes.

Key issues

Let us now consider some of the other possible issues for Mrs B in this situation and the role of the multidisciplinary team. Key issues include assessment of cognition and degree of impairment to determine the capacity for decision making in a person with unstable diabetes. For example, when considering memory:

- When you provided Mrs B with information about her changed treatment regimen, did she retain the instructions later in the session?
- Did she recall the information at your next visit?
- Did her memory improve if she received the information a number of times?
- Was her memory improved with visual aids (e.g. written material or simple visual diagrams)?

When considering her executive function:

- Does Mrs B understand the implications of maintaining her community supports?
- Can she voice the risks and benefits of continuing these supports and appreciate the ramifications of relinquishing these supports in the community?

Other factors that will inform the care plan:

- Assessment and management of carer stress.
- Consideration of the trade-offs between optimal management of diabetes in a supervised setting in comparison to what is possible at home in the community.
- Understanding the importance of establishing and specifying clear goals for glycaemic management, which has to be balanced with what would be the acceptable upper and lower blood glucose levels in this situation.
- Determination of strategies that address high-demand clinical tasks in a person with substantial cognitive impairment and threshold for entry into long-term care.

Members and roles of individuals within the multidisciplinary team

Fortunately, multidisciplinary team members include a broad range of healthcare professionals, such as medical staff, nursing staff, pharmacists, physiotherapists, occupational therapists, neuropsychologists, social workers, dietitians, and speech therapists. This is not a complete list of disciplines, as the composition of the team depends on the individual's demographics and clinical conditions being managed. For example, a multidisciplinary team for people with diabetes would include a diabetes educator and dietitian, who provide education and advice on using diet and insulin dosing. The broader the skill base of the team, the more holistic the provided treatment will be, resulting in better personalized care. In the case of Mrs B, we will examine the roles of the physiotherapist, occupational therapist, and neuropsychologist.

Physiotherapist

The physiotherapist would monitor and treat Mrs B for the fractured ankle, seeking to improve her transfers and mobility, with the aim of reaching independence (with or without a mobility aid).

This level of independence reduces the care burden in the community and assists with promoting regular physical activity as part of the management of her diabetes. If Mrs B is unable to become independent, the role of the physiotherapist is to provide education and training to her caregiver on how to safely support Mrs B to transfer to and mobilize at home. Ongoing physiotherapy review within the home environment is valuable to promote independence and address the home environment changes needed to accommodate a new mobility aid. Home-based physiotherapy would also encourage and establish a regular schedule of exercise to maintain mobility and prevent decline.

Occupational therapist

An occupational therapist's role is to determine the person's premorbid level of function and routines, which include the level of support and assistance in care. This knowledge assists in determining realistic goals for discharge.

An occupational therapist will thoroughly assess the person's function, through standardized and functional assessments in different care settings. A functional assessment provides a wealth of information about the person's physical capabilities, as well as their cognitive abilities within a routine task; for example, the task of making breakfast, which requires planning and execution of multiple different tasks.

Due to her poor mobility, Mrs B was unable to safely complete her personal or domestic activities of living and would require the assistance of her husband and formal carers to complete these tasks at home.

Mrs B's ability to self-manage her diabetes requires identifying the multiple and separate physical tasks and cognitive functions. For example, does Mrs. B have the physical capability to

- Use the blood glucose meter?
- Read the result?
- Draw up insulin?

Does she have the cognitive capability to:

- Recognize the blood glucose meter?
- Interpret the blood glucose level?
- Determine how much insulin to administer?

These tasks and assessments of capability and reliability are often shared between the occupational therapist and nursing staff, who are able to monitor whether Mrs B is retaining the information from one day to the next.

The primary intention is to determine if the person is able to carry out these tasks independently. If this is not possible, due to physical (hand dexterity or visual impairment) or cognitive (poor problem solving or memory) deficits, the team would then look to family or carers to determine if they could complete the tasks.

The process is carried out with the family member in the same way, to ensure they have the physical and cognitive capacity to complete the tasks. With Mrs B, her husband was worried about

administering insulin correctly and requested this be completed by a community nurse. Occupational therapists would also work with the person in the community to ensure their environment is well set up to meet the person's safety requirements, but also provide cognitive assessment and intervention. This could include providing visual prompts or alert systems to remind the person to check their blood glucose levels and administer insulin.

Neuropsychologist

To assist the multidisciplinary team to better understand the strengths and deficits of a person's cognition, a referral should be made to a neuropsychologist. Neuropsychologists are clinical experts in determining a person's premorbid level of cognition and what degree of decline has occurred in the different cognitive domains.

Neuropsychologists assess all areas of cognitive function, to provide information to the multidisciplinary team as to what areas of strength a person still possesses and where there has been the greatest decline. This assists the multidisciplinary team in identifying and using a person's strength to continue to function as independently as possible. With Mrs B, a neuropsychology assessment provided clear evidence of substantial cognitive decline in multiple domains, which supported the guardianship application.

Key learning points

It is important to recognize early in the hospital admission if a person has complex medical and care needs. This enables referral to appropriate community programmes to support the person's transition from hospital to home. An optimal community programme is one that has a holistic approach with a broad range of medical, nursing, and allied health professionals.

- Mrs B has a complex diabetes treatment regimen and significant care needs. For long-term care in the community to be sustainable, engagement and support for her caregiver are essential. It is vital to explore what barriers have led to disengagement by a carer and consider how to overcome these.
- Transition to the community is a good opportunity for medical practitioners to review the appropriateness of glycaemic targets. The goals of treatment may need revising, especially in context of Mrs B's goal of remaining at home.
- It can be invaluable to have carers attend the hospital to practise the care routines required for when a person returns home. This ensures the team is aware of the person and carer's capabilities as well as the dynamic between them. For example, Mr B could be provided with education including prompt sheets on how to manage Mrs B's blood glucose levels and symptom management. This would be reviewed once again when Mrs B returns home.

Case Study 64.3 Promoting self-care

Mr C was a 71-year-old man who lived at home, supported by his son and daughter who lived nearby and visited twice daily. Past medical history included dementia, previous stroke, a heavy smoker of up to 30 cigarettes a day, and a heavy drinker of alcohol, complicated by pancreatitis and diabetes, for which he was treated with twice-daily insulin.

Over the past few years, Mr C's mobility and manual dexterity had declined to a level where he was house-bound and was no longer able to visit the local bar for a drink. Complicating the situation further, Mr C also suffered stiffness and paralysis in one arm and difficulties using his other hand.

Mr C had given up cigarette smoking, but wanted to continue drinking alcohol as he claimed this was the only activity in life he enjoyed. Mr C wanted to drink more than health guidelines recommend and required his children to purchase the alcohol. His children supplied meals and assistance with shopping; however, Mr C's intake was erratic and there was often spoiled food in the fridge.

Community nursing supported Mr C with administering insulin morning and night, although Mr C did not monitor his blood glucose levels. Nurses also assisted with personal care and noted that Mr C had small pressure injuries on his sacrum and was malnourished, having lost 7 kg in the past 12 months. Visiting nurses noted increasing occasions of Mr C declining to take medication, food, or fluids.

Individuals with chronic diseases often have difficulty with self-managing their condition, and this inability increases their burden of care and hospitalization [16]. As described earlier, self-management includes problem solving, decision making, resource utilization, interacting with healthcare providers, and taking action [58]. It also requires the person to actively participate in their day-to-day treatment and management [58].

In this case study 64.3 of Mr C, we again confront the chronology of his past medical history. Which came first: the diabetes or the dementia? As we can see, diabetes may arise from pancreatitis due to chronic alcohol overuse, which also causes cognitive impairment. We also see that different aetiologies for cognitive impairment may occur in the same person.

Although Alzheimer's disease is the most common form of dementia and typically is associated with older age, dementia in a younger person may be due to vascular disease related to cigarette smoking, and cognitive impairment exacerbated by alcohol overuse.

Key issues

Let us now consider some key issues for Mr C in this situation:

- Mr C has stated that he wants to continue drinking alcohol, as he considers this as enhancing his quality of life.
- Alcohol is detrimental to his cognitive and physical function and creates a tension for clinical staff around how to address their duty of care.
- The presence of dementia may affect his ability to make decisions and so there is a need to assess the nature and extent of cognitive impairment. Given the extent of vascular risk factors, Mr C's executive function is likely to be compromised. Deficits in this domain are frequently under-recognized.

When considering executive function:

- Consider a formal cognitive screening tool, such as the MoCA.
- Is executive dysfunction hampering his ability to appreciate the impact of his life choices on his health?
- Could self-monitoring deficits, commonly seen in executive dysfunction, affect his ability to manage his blood glucose levels?

Given that Mr. C has already had a stroke, what other domains are affected?

- His manual dexterity may be compounded by changes in visual spatial function.
- What about his language function?

When considering language function:
- Has he understood the instructions provided to check his blood glucose levels?

When considering his visual spatial function:
- Did he have the necessary visual spatial ability to utilize the equipment required to monitor his blood glucose levels?

Other issues include:
- There is evidence of self-neglect, in that Mr C is declining to take medication, food, or fluids and is losing weight.
- There is an ongoing need for community supports and the potential for resistive or antisocial behaviour if Mr C is inebriated when nursing staff attend.
- There is suboptimal management of Mr C's diabetes and the development of pressure injuries.

Once again, the multidisciplinary team would complete standardized and functional assessments to determine Mr C's areas of cognitive strength and spend time with him to determine his health and lifestyle goals.

Clinical dilemmas

The key clinical dilemmas in brief include a choice between the following:
- Respecting Mr C's lifestyle choices and desire to live at home, which are likely to lead to suboptimal clinical outcomes with unstable diabetes and ongoing decline in his health status.
- Seeking to implement feasible but suboptimal clinical interventions at home, which Mr C may choose to ignore and potentially cause a breakdown in the therapeutic relationship.
- Seeking a guardian to enforce Mr C relocating to a long-term care facility with its highly controlled environment that could implement optimal clinical interventions, but conflicts with Mr C's lifestyle wishes.

Clinical approach

The key starting point for the multidisciplinary team is to assess and utilize Mr C's cognitive strengths to assist him to reach his goals. This also requires determining if he understands the consequence of continuing to drink alcohol in excess, as this will likely cause deterioration in cognitive function, increase his risk of falls, worsen glycaemic levels, and potentially create an antisocial environment for community health staff.

In this situation, assessment of his cognitive function, mental state, and premorbid personality by a medical practitioner and neuropsychologist would be beneficial to inform the decision-making process. In addition, a trial period at home would assist in separating the perceived from the real risks to Mr C's situation. This is important, as healthcare professionals may be paternalistic and defensive in their approach to decision making because of legal concerns about breaching their duty of care.

The next step is to consider the existing and any new interventions that would provide a comprehensive approach to assist Mr C to achieve his goals. As stated, Mr C was receiving assistance from visiting nurses for personal care tasks and to administer insulin. Family members were also visiting twice daily, helping with domestic and community tasks. This use of formal services is consistent with a self-management model, as it encompasses resource utilization and interaction with healthcare providers.

The neuropsychologist within the multidisciplinary team along with the community nurses could develop strategies to compensate for any deficits in Mr C's cognitive function. This may include:
- Referrals to a dietician to optimize nutritional intake.
- Developing a system to ensure Mr C is eating adequately, such as having 'meals on wheels' delivering a hot midday meal to encourage Mr C to eat during the day.
- Visual aids and a diary to remind Mr C of his appointments.
- Technology aids to assist with medication taking.
- Ensuring Mr C's family are aware of his cognitive changes and how these may affect his day-to-day care.
- Surveillance of Mr C's health status, given he appears to lack insight into the significance of the sacral pressure injury.

The aim of a multidisciplinary team is to maintain the person's independence and their ability to remain at home safely if this is their wish. To do this, it is pertinent that the multidisciplinary team fully understands the person's cognitive profile. This serves three functions. First, it allows the formulation of strategies to assist the person in proactively participating in their own self-care; second, it identifies deficits that need to be addressed through other services; and third, it assists in developing appropriate contingency plans.

When chronic diseases such as diabetes are self-managed appropriately, it slows the cognitive decline and therefore people maintain their independence within the community.

Key learning points

- It is important to consider and evaluate mood for comorbid depression. Mr C has several risk factors (including chronic disease, previous strokes, alcohol dependence, and social isolation) and depression may be complicating his current presentation.
- There are various risk factors for cognitive impairment. Mr C has previous strokes, diabetes, and ongoing alcohol dependence. An understanding of his cognitive strengths and deficits will help guide treatment plans and discussions with him about his long-term goals.
- Completing a home assessment with an occupational therapist prior to returning home would allow an opportunity to enhance the environment to support a person's independence; for example, utilizing small hand aids to compensate for the reduction in manual dexterity.
- Collaboration of the occupational therapist with the community nurse to monitor and actively treat the pressure injuries would include assessing for appropriate equipment for Mr C's seating and mattress. The team should ensure the equipment complements Mr C's cognitive abilities and lifestyle choices.

Case Study 64.4 Prevention of cognitive decline

Ms D was an 83-year-old woman who lived in a nursing home and required assistance with activities of daily living (including administration of medication). She had a past medical history of Parkinson's disease, depression, ischaemic heart disease, a cardiac pacemaker, and type 2 diabetes.

Her medications include co-beneldopa (benserazide hydrochloride and levodopa), long-acting insulin, aspirin, metoprolol, atorvastatin, amitriptyline, and gliclazide MR.

One day at approximately 11 a.m., a junior nurse entered Ms D's bedroom to find her unconscious with a blood glucose reading that was profoundly hypoglycaemic. Ms D was admitted to hospital for further treatment and investigation, where aspiration pneumonia was diagnosed.

In this case study 64.4 of Ms D, we consider the challenges of preventing further cognitive decline, the role and the importance of appropriate glycaemic targets, and avoiding hypoglycaemia.

Key issues

Let us consider some key issues for Ms D in this situation:

- What comorbidities could affect Ms D's cognitive function?
- What is the impact of medication on the management of underlying conditions?
- What glycaemic goals might be appropriate for Ms D?

Comorbidities

Ms D has Parkinson's disease, multiple vascular risk factors including diabetes, and is prescribed multiple medications, which could all contribute to progressive decline in cognitive function. Identifying reversible factors is essential to optimize care and long-term function. One prevalent and potentially reversible comorbid condition is depression.

Depressive symptoms are highly prevalent in older adults with diabetes and are significantly correlated with poorer cognition [59]. People with comorbid depression and diabetes are 3.5-fold more likely to develop dementia compared with those with either condition alone [60]. Regular screening and evaluation for mood symptoms using validated tools (such as the Geriatric Depression Scale) are recommended.

Cardiovascular risk factors

The pathogenesis of cognitive decline in diabetes is multifactorial, and preventive measures need to address more than just glycaemic goals. Older people with diabetes are at increased risk of cardiovascular disease and stroke.

Management of lipid and blood pressure to individualized targets is recommended, as is lifestyle management, including optimal nutrition, smoking cessation, moderate alcohol intake, and exercise [61]. However, it is important to recognize that behavioural change may be difficult to implement in the setting of cognitive impairment (especially executive dysfunction) and that making small changes or enlisting help from caregivers can be useful strategies [62].

Aspirin therapy (while not recommended for the prevention of cognitive decline) may be appropriate for primary or secondary prevention of other cardiovascular diseases.

Medication

Medication errors

Although this information about medication and polypharmacy will be familiar, it is worth restating:

- Individuals with diabetes co-beneldopa require frequent monitoring of blood glucose levels and possible dose adjustment of anti-diabetes agents.
- As the medication regimen becomes more complex, the risk of the person becoming hypoglycaemic increases.
- The risk of medication errors increases with the number of medications prescribed.
- Cognitive impairment alters Ms D's ability to identify herself to staff, increasing the risk of errors due to misidentification. Also, she is no longer able to check what is being administered.

Anti-diabetes agents and cognitive health

No specific anti-diabetes agents have been shown to reduce the risk of dementia in diabetes [63]. However, treatment goals may influence the choice of pharmacotherapy. Agents with a lower risk of hypoglycaemia are preferred in older adults.

Cholinesterase inhibitors and N-methyl D-aspartate antagonists

Cholinesterase inhibitors (rivastigmine, donepezil, and galantamine) and N-methyl D-aspartate (NMDA) antagonists (memantine) are the only currently recommended medications for the treatment of Alzheimer's dementia. These agents may result in modest improvements in cognition and function in mild to moderate Alzheimer's dementia, although their use can be limited by gastrointestinal side effects and headaches [64]. Cholinesterase inhibitors are underprescribed in older people with diabetes and dementia, even though their use reduces mortality in this cohort [65]. Use of these cognitive enhancers in people with diabetes could help in the self-management of diabetes, preventing further cognitive decline.

Glycaemic goals and maintaining cognitive health

Strict glycaemic targets are fundamental to preventing end-organ damage in diabetes, but a more considered approach is required when it comes to preventing dementia. Chronic hyperglycaemia (HbA_{1c} levels >7% [53 mmol/mol]) has been associated with an increased risk of cognitive impairment and further decline in older adults with diabetes [66]. However, the older person's brain is also vulnerable to the effects of neuroglycopaenia.

Episodes of severe hypoglycaemia are associated with an increased risk of developing dementia, independent of HbA_{1c} [67]. The American Diabetes Association has suggested individualized treatment targets in older adults with diabetes. Practice guidelines [61] recommend a glycaemic goal of:

- HbA_{1c} of <7.5% (58 mmol/mol) in those with few medical comorbidities and intact cognitive and functional status.
- HbA_{1c} of <8–8.5% (64–69 mmol/mol) in frailer older adults, with multiple chronic diseases, cognitive impairment, or functional dependence.

To identify the appropriate treatment strategy, regular cognitive screening is vital. Established cognitive impairment is a risk factor for reduced self-care and severe hypoglycaemic episodes [16, 68] and thus further cognitive decline. Recognizing the correct glycaemic targets and supported self-management to achieve these goals is crucial for maintaining cognitive health, functional independence, and self-care.

Key learning points

- Re-evaluating glycaemic management plans should occur at least annually. This should be a comprehensive assessment, taking into account cognitive screening performance and lived experience.
- Polypharmacy is common in older adults and increases risks of drug interactions, medication errors and omissions, falls, and cognitive impairment.
- Social isolation is a risk factor for cognitive decline and dementia. Residents in nursing homes may still experience social isolation. A healthcare professional should spend time with Ms D to determine her interests and abilities to enhance social interaction and activity.
- Often there is an assumption that a nursing home is designed and equipped for the needs of residents. This is not always the case. It is important that residents are assessed to ensure their environment meets their needs. This is especially true for residents with cognitive impairment, who may not be able to voice their concerns or needs. This may include review of their seating, overall set-up and access, and ability to use a call bell. It is important, given Ms D's diagnosis of Parkinson's disease, that she is able to use the bell, to alert staff if she is feeling unwell and facilitate a timely response.

Conclusion

People with declining cognitive function and diabetes are at a greater risk of chronic hyperglycaemia because they have difficulties with learning and retaining new knowledge, the inability to recognize the importance of self-care, which involves planning and organizing daily tasks to optimize control, and may lack the motivation to adhere to care plans.

Clinicians need to be aware of the onset, presence of, and impact of dementia in persons with diabetes. Rather than a classic presentation of *forgetfulness*, the onset of dementia may manifest in the person not retaining information relevant to diabetes, having an inability to learn insulin adjustment skills or perform insulin injections, and missing clinical appointments.

The presence of dementia as a comorbid condition must be integrated into decisions and care planning. However, it should not detract from seeking to achieve optimal management.

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65 Mental Disorders and Diabetes

Najma Siddiqi[1,2], Marietta Stadler[3], and Richard I.G. Holt[4,5]

[1] Department of Health Sciences, University of York and Hull York Medical School, York, UK
[2] Bradford District Care NHS Foundation Trust, Bradford, UK
[3] Department of Diabetes, School of Cardiovascular and Metabolic Medicine and Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK
[4] Human Development and Health, University of Southampton, Faculty of Medicine, Southampton, UK
[5] Southampton National Institute for Health Research Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK

Key points

- The interactions between diabetes and mental disorders are bidirectional and complex: diabetes raises the risk of mental disorders, but mental illness and its treatment with certain psychotropic medications also increase the risk of diabetes.
- The prevalence of diabetes is increased two- to threefold among those with mental disorders, including in depression, anxiety, and psychotic illnesses.
- The mechanisms underlying the association between diabetes and mental illness are multifactorial and include genetic and environmental factors, as well as effects of the disorders and their treatments.
- The presence of comorbid diabetes and mental illness worsens outcomes for both conditions. The rates of microvascular and macrovascular complications, acute metabolic dysregulation, and diabetes-related deaths are all higher in people with mental illness; and the severity of and recovery from mental disorders are adversely affected in the presence of diabetes.
- Since mental health problems are more common among people with diabetes, heightened levels of awareness and knowledge about mental disorders are vital for the healthcare professionals who work with them.
- Screening for mental health problems should form part of the holistic care of people with diabetes; the availability of mental health expertise in the settings where people with diabetes are treated is generally poor and should be improved.
- Weight management in people with psychotic illnesses is essential to tackle overweight and obesity related to these conditions and help reduce the incidence of diabetes. Tailored lifestyle interventions have been shown to reduce body weight in selected people with psychosis. Several drug therapies promote weight reduction in people taking antipsychotic drugs. These interventions should be offered to people with psychotic disorders.
- Effective diabetes management, incorporating primary care, diabetes services, and mental health teams working together, is essential to reduce the poorer health outcomes and current inequity experienced by people with mental illness and diabetes.

The greatest challenge facing medicine in the twenty-first century is multimorbidity, defined as any combination of chronic disease with at least one other disease (acute or chronic) or biopsychosocial factor (associated or not) or somatic risk factor in the same individual [1]. While diabetes healthcare professionals are used to managing this increasingly common challenge, given the effects of diabetes on many body systems, the comorbidity of diabetes and mental illness is less well appreciated, despite being common and worsening the outcomes of both conditions [2]. Mental illness may hinder an individual's ability to undertake the diabetes self-management that is central to the maintenance of health and prevention of complications and premature mortality. Therefore, an understanding of the complex interaction between physical and mental health is crucial to the management and outcome of people with diabetes.

Both diabetes and mental disorders are common conditions, and therefore a degree of co-occurrence would be expected purely by chance. There is considerable evidence, however, that diabetes is associated more frequently than expected with a range of mental disorders. In particular, it appears that people with common mental disorders, including depression, anxiety and eating disorders, and psychotic disorders such as schizophrenia and bipolar affective disorder, are at increased risk of developing diabetes [3, 4]. Furthermore, those with diabetes go on to develop a range of psychological problems at increased rates compared to those without diabetes [4]. This was noted over a century ago; in his celebrated textbook *Pathology of Mind*, Henry Maudsley wrote: 'Diabetes is a disease which often shows itself in families in which insanity prevails. Whether one disease predisposes in any way to the other or not, or whether they are independent outcomes of a common neurosis, they are certainly found to run side by side, or alternately with one another more often than can be accounted for by accidental coincidence or sequence' [5].

Unfortunately, in most countries healthcare services are poorly equipped and organized to deliver high-quality care for both

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physical and psychological needs in the same setting [6]. Clinicians need to be aware of the increased risks of comorbidity and the need for screening. Diabetes healthcare professionals should be able to provide *first-response* management for mental health problems, and recognize the needs of those with more complex problems for whom specialist management is essential. The topic of multimorbidity has attracted interest from researchers, and considerable progress has been made in understanding the epidemiology and psychosocial and biological mechanisms involved. Efforts targeting mental health and primary care providers have increased awareness of diabetes and metabolic problems in general, and have led to initiatives to increase routine screening and referrals for diabetes specialty care for people with mental disorders, with varying degrees of success [7].

This chapter will provide an overview of the relationship between diabetes and mental illness, in particular focusing on the association with depression, anxiety, eating disorders, and psychotic illness (schizophrenia and bipolar illness). Within each section, the epidemiology of the comorbidity, mechanisms underlying the association, and clinical implications will be considered.

Depression

The association between diabetes and depression has been recognized for many years. In the seventeenth century, Thomas Willis described how 'diabetes is a consequence of prolonged sorrow' [8]. Nevertheless, depression is a frequently ignored component of holistic diabetes care. Until the last decade, any discussion of mood disorders and diabetes would have concentrated solely on the increased rates of depression in people with diabetes, and is likely to have viewed such comorbidity as an 'understandable' reaction to the difficulties resulting from living with a demanding and life-limiting chronic physical illness. We now understand that the relationship between the two conditions is more complex than this:

- At least in the case of type 2 diabetes, the relationship between diabetes and depression is bidirectional, as depression is a risk factor for the development of diabetes [9–11].
- Biological aspects of diabetes may contribute to the development of depression and vice versa.
- Other antecedent factors, such as the early nutritional environment or neighbourhood, may contribute to the risks of both conditions [4].

Given the large numbers of people with diabetes and depression, ~10% and 4.4% of the total world's population, respectively, and the twofold higher rates of depression in people with diabetes [12], the comorbidity of these two conditions presents a major clinical challenge as the outcomes of both are worsened by the presence of the other. Quality of life is worse, diabetes self-management is impaired, the incidence of complications is increased, and life expectancy is reduced [4]. The costs of treatment increase significantly both for individuals with the comorbidity and for health economies, but these costs do not necessarily result in significant improvements in disease or quality-of-life outcomes [13].

Case definition

Depressive symptoms exist on a continuum of severity. Standard definitions of *clinical* depression are based on symptom count and duration; the most widely used diagnostic criteria in current practice are those of the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) major depression (Table 65.1) [14]. This definition approximates to a level of symptomatology that is associated with significant disability and dysfunction, but it is important to note that depressive symptoms of lesser severity may still compromise self-care and outcomes in people with diabetes.

Table 65.1 DSM-5 criteria for a major depressive episode.

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood, or (2) loss of interest or pleasure.
   1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful).
   2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
   3. Significant weight loss when not dieting or weight gain (e.g. a change of >5% of body weight in a month), or decrease or increase in appetite nearly every day.
   4. Insomnia or hypersomnia nearly every day.
   5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
   6. Fatigue or loss of energy nearly every day.
   7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
   8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
   9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hypothyroidism).

Source: American Psychiatric Association 2013 [14].

The clinical category of mood disorders includes both unipolar depression and bipolar (previously known as *manic-depressive*) illness. This section will focus on unipolar depression; bipolar illness will be included in the section on psychotic disorders.

Epidemiology

Depression is common, affecting between 3% and 5% of the general population at any time. Between 1990 and 2017 globally, its incidence increased by 50% to 3.25 per 1000 (age-standardized rate) [15]. Depressive disorders are now ranked as the single largest contributor to non-fatal health loss (7.5% of all years lost to disability) [16].

Considerable variability in measurement and use of terminology has contributed to heterogeneity and inconsistency in studies examining diabetes and depression [4]. The meaning of the term *depression* spans relatively minor, occasional negative mood states (which should more accurately be termed *depressive symptoms*) to incapacitating and treatment-resistant disorders that fulfil all diagnostic criteria for clinical depression. Many self-rating scales do not acknowledge the overlap between symptoms of diabetes and

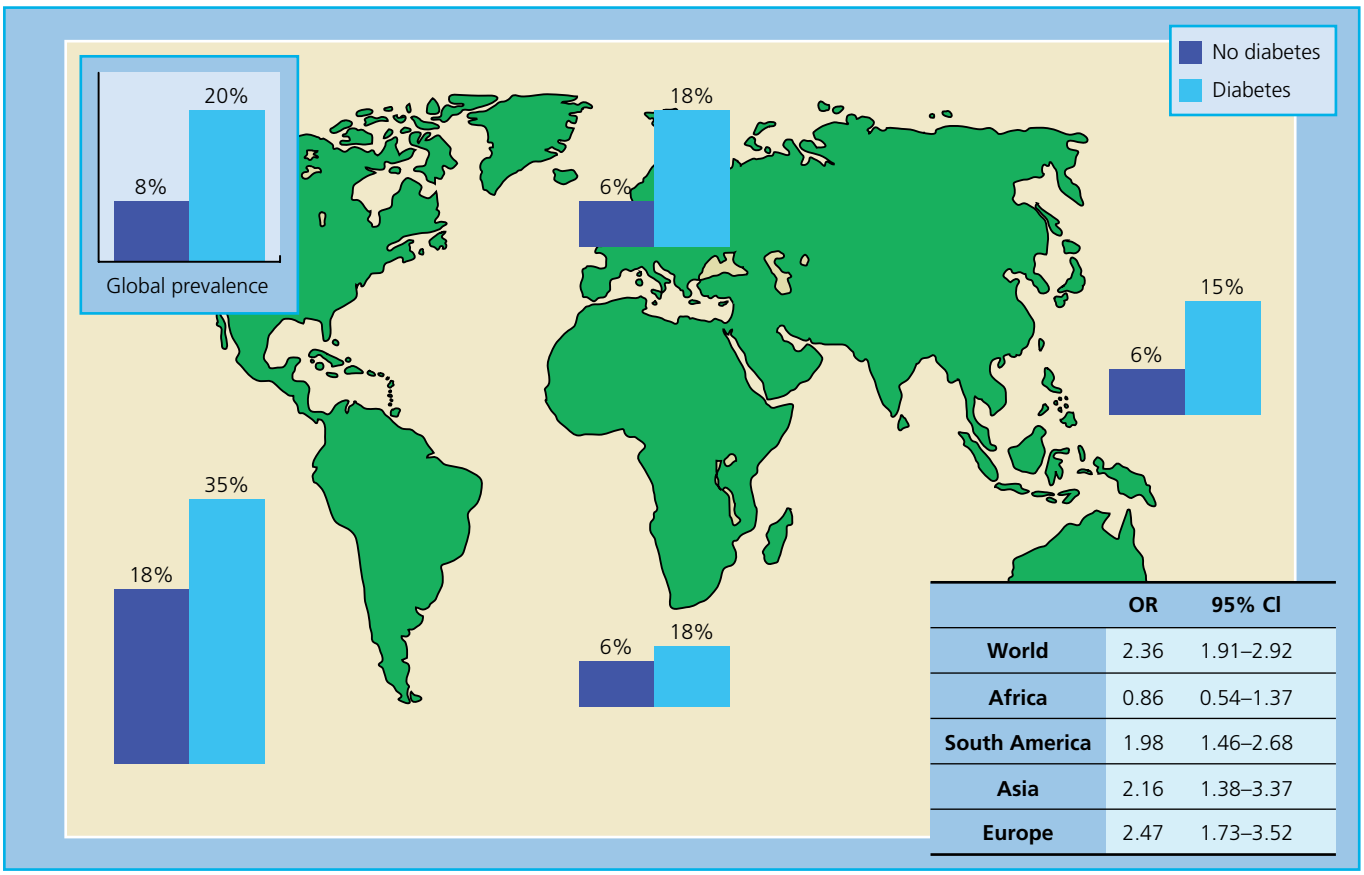
those of depression (e.g. fatigue, weight loss), potentially leading to overestimates of the prevalence of depression in those with diabetes [17]. The gold standard for ascertainment of case status is a research diagnostic interview; at most, rating scales can only give a probabilistic estimate of caseness. A further confounding factor is the construct of *diabetes-related distress*, which captures the emotional distress associated with living with diabetes [18]. Diabetes-related distress correlates modestly with depressive symptoms with ~30% overlapping variance, but remains distinct from depression in its association with self-management and glycaemic levels.

Studies have tended to ignore the heterogeneity of diabetes, studying mixed populations of different forms of diabetes (e.g. type 1 diabetes and type 2 diabetes). It is important to distinguish between these groups for several reasons:

- People with type 2 diabetes are generally older and depression prevalence varies with age.
- Pathological mechanisms may differ.
- The rates of diabetes-related complications and other comorbid conditions such as obesity and heart disease differ.
- Management demands are different.

Studies have often been based on *convenience* samples, usually drawn from specialist diabetes clinics, where referral patterns and the effect of other biases in sample composition, such as ethnicity, were unknown. Finally, studies often have low or unknown response rates, and since the presence of depressive symptoms may reduce the likelihood of responding in such studies, this biases prevalence estimates further. More recent studies using better methods, and meta-analyses, have tended to report lower estimates of prevalence.

In a meta-analysis of 44 studies, the prevalence of depression was more than doubled in people with type 1 diabetes compared with the general population (22% vs 13%), while for people with type 2 diabetes the rates were increased by 55% (19% vs 11%) [19]. The prevalence of depression in people with diabetes was higher in studies carried out in specialist care (36%) than in those in community or primary care (12%). The same meta-analysis also reported higher rates of depression in low- and middle-income countries compared to countries with high-income economies [19], a finding that was also reported in another meta-analysis of 248 observational studies including over 8 million people with type 2 diabetes. The pooled prevalence of depression across the world was 28%, but this varied across regions; studies from Asia and Australia reported the highest rates while those from Europe reported the lowest values [20]. Despite these regional differences, the association between diabetes and depression appears to be a significant issue across many countries; in a study including 231 797 adults from 47 countries, people with diabetes were more than twice as likely to have experienced an episode of depressive symptoms than those without (Figure 65.1) [21]. Similar to what is observed in the general population, the prevalence of depression is higher among women with diabetes compared with men with diabetes (34% vs 23%) and among those under 65 years [20].



	OR	95% CI
World	2.36	1.91–2.92
Africa	0.86	0.54–1.37
South America	1.98	1.46–2.68
Asia	2.16	1.38–3.37
Europe	2.47	1.73–3.52

Figure 65.1 Depressive episodes in people with and without diabetes. Odds ratios (OR) of an episode of depressive symptoms according to diabetes presence with 95% confidence intervals (CIs). Source: Data from Mommersteeg et al. 2013 [21].

The course of depression has been studied in 2460 people with type 2 diabetes in a primary care setting [22]. Over a three-year period, 26% met the criterion for depression on at least one occasion, with incident depression present in 14%. Recurrence or persistence of depression was evident in 66% of those with baseline depression. Depression was more common in women and those with low education, non-cardiovascular chronic diseases, stressful life events, or a self-reported history of depression. A meta-analysis of 11 cohort studies including ~50 000 people with type 2 diabetes but without depression at baseline indicated that the incidence of depression is 24% higher in people with diabetes [10], while another meta-analysis of 13 studies found that incident depression was increased by 15% in people with diabetes at baseline [11]. The discrepancy between prevalence and incidence rates may be explained by the greater persistence of depression and higher relapse rates in people with diabetes.

The prevalence of depression is also increased in children and adolescents with type 1 diabetes or type 2 diabetes. A meta-analysis of 109 studies involving 52 493 children with diabetes found that the prevalence of depression was 22.2% among children with type 1 diabetes and 22.7% in children with type 2 diabetes [23]. Consistent with studies in adults, the prevalence of depression was higher among girls (29.7%) than boys (19.7%) and in low- to middle-income countries (29.3%).

Depressive disorders as a risk factor for diabetes

A meta-analysis of nine cohort studies found that adults with depression had a 37% increased risk of developing type 2 diabetes [9] after accounting for factors common to both disorders, including sex and body mass index (BMI). There is heterogeneity across studies, which in part could be ascribed to ascertainment bias. It is also worth noting that people with depression may be more likely to be screened for diabetes than those without, so studies relying on routinely collected healthcare data may overestimate the difference in diabetes risk between people with depression and the general population.

Which people with diabetes are likely to develop depression?

Risk factors for depression in otherwise healthy individuals, including female sex, marital status, childhood adversity, and social deprivation, operate equally in people with diabetes and much depression in people with diabetes may be *independent* of the presence of the disease. However, there are both treatment- and diabetes-specific risk factors associated with depression. The use of insulin in type 2 diabetes is associated with higher rates of depression compared to non-insulin medications or dietary and lifestyle interventions alone; a meta-analysis of 28 studies reported an overall 59% high risker of developing depression in people taking insulin, or a 42% higher risk when compared with other oral antidiabetes agents [24]. It seems unlikely that insulin causes depressive symptoms *per se*, but insulin is associated with increased treatment demands and is generally used in people with more advanced disease. The intensive self-monitoring of blood glucose required with insulin therapy may also adversely affect depressive symptoms [25]. Recurrent hypoglycaemia and elevated glycated haemoglobin (HbA_{1c}) are both risk factors for depression and insulin therapy is usually associated with greater glycaemic variability than other treatments. Again we can see evidence of the bidirectional relationship between diabetes and depression: in a 10-year study of 3742 people with type 1 diabetes requiring emergency room visit or hospitalization, those admitted with a hyperglycaemic or hypoglycaemic event were 1.4-fold and 74% more likely to develop depression, respectively. Conversely, the 20% with depression at baseline had a 2.5-fold increased risk of hospitalization for a severe hyperglycaemic episode and an 89% increased risk of severe hypoglycaemia [26].

There is a well-recognized association between cardiovascular disease and depression [27], but the development of microvascular complications, particularly sexual dysfunction and painful peripheral neuropathy, are also associated with depression [28, 29]. In a specialized outpatient clinic, the presence of two or more complications more than doubled the risk of depression in people with type 2 diabetes, with neuropathy and nephropathy showing the strongest association [30].

Proposed mechanisms linking depression and diabetes

Several psychological, sociological, and biological models have been proposed to explain the association between diabetes and depression. While there may be specific reasons why one condition predisposes to the other, recent research has also considered common antecedents to both (Figure 65.2) [4].

Common antecedents

An adverse intra-uterine environment may predispose individuals to both type 2 diabetes and depression. There is a J-shaped relationship between birth weight and plasma glucose, insulin concentrations, and type 2 diabetes, while some but not all studies have shown that fetal undernutrition is associated with adult depression [4]. One possible mechanism is programming of the hypothalamic–pituitary adrenal (HPA) axis, as both depression and diabetes are associated with HPA dysfunction [31]. Adverse environmental factors in postnatal life, ranging from childhood adversity to neighbourhood environment and poverty, may also influence the predisposition to depression and diabetes.

Why diabetes may increase the risk of depression

The traditional view holds that depression is an understandable reaction to the challenges of living with a demanding chronic physical illness that is associated with disabling complications and premature mortality. This was supported by an early meta-analysis that found no increase in depression rates among those with undiagnosed diabetes or impaired glucose metabolism [32]. A more recent meta-analysis of 20 studies, however, found that compared with individuals with normal glucose metabolism, the prevalence of depression was moderately increased in those with undiagnosed type 2 diabetes (odds ratio [OR] 1.27, 95% confidence interval [CI] 1.02 to 1.59), but more markedly increased in those with previously diagnosed type 2 diabetes (OR 1.80, 95% CI 1.40 to 2.31) [33]. As the prevalence of depression is higher following a diagnosis of diabetes, this suggests that the knowledge of the diagnosis and the burden of managing the condition and its complications are important in the aetiology of depressive symptoms, but are not the only factors; nevertheless, healthcare professionals need to convey the diagnosis of diabetes sensitively and provide psychosocial support to mitigate against this effect.

Other factors could include biological mechanisms, as it is well recognized that both hypoglycaemia and hyperglycaemia affect brain function in the areas involved in cognition and mood [34].

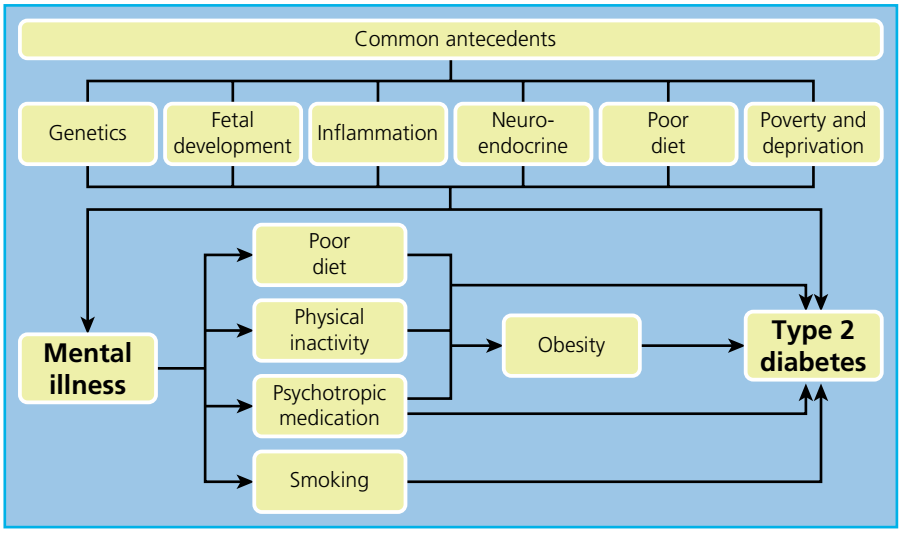


Figure 65.2 Mechanisms that explain why mental illness may predispose to type 2 diabetes and vice versa. There are a number of common antecedents that increase the risk of both conditions. Once an individual develops mental illness, other health behaviours may occur, which together with the effects of psychotropic medication may further increase the risk of diabetes, either directly or indirectly through the development of obesity. Source: Modified from Holt and Mitchell 2015 [3]. Copyright 2015 Nature Publishing Group.

Animal studies of diabetes have shown loss of hippocampal integrity and neurogenesis, which may contribute to mood symptoms, while in humans, MRI studies have shown hippocampal atrophy. Prefrontal glutamate-glutamine-γ-aminobutyric acid levels are increased in people with type 1 diabetes in a way that correlates with mild depressive symptoms [35].

Why depression may lead to diabetes

People with depression tend to be more sedentary and eat diets that contain more saturated fats and refined sugars and less fruit and vegetables than the general population [36, 37]. Other self-care behaviours may also be relevant; a meta-analysis found that people with depression were significantly less likely to follow diabetes treatment recommendations including missed medical appointments, medication use, glucose monitoring, and foot care [38]. This could lead to a vicious cycle whereby poorer self-care management leads to hyperglycaemia, which in turn worsens depressive symptoms and consequently contributes to less effective diabetes self-care. Depression is associated with disrupted sleep patterns [39], which may increase insulin resistance and risk of type 2 diabetes [40].

Pharmacological treatment of depression has also been implicated in the development of diabetes; some antidepressants may cause significant weight gain, which may worsen insulin resistance [41]. Case reports and observational studies have shown a consistent association between the use of antidepressants and diabetes, while randomized controlled trials (RCTs) have reported both hyperglycaemic and hypoglycaemic effects [42]. It is uncertain, however, whether any or all antidepressants cause diabetes, as their use may be a marker of individuals at high risk of diabetes.

Consequences of depression in diabetes

Comorbid depression adversely affects diabetes outcomes and decreases quality of life [43–45]. This is not explained by hyperglycaemia as, rather surprisingly and in contrast to diabetes-related distress, no consistent association between depressive symptoms and HbA_{1c} has been found [46–48]. Nevertheless, treatment studies suggest that improving glucose levels may accompany a reduction of depressive symptoms [49].

Depression is associated with worsened severity and incidence of many diabetes complications. Again we see a bidirectional relationship, as not only are those with diabetes complications at increased risk of diabetes, but people with diabetes and depression are at increased risk of developing both microvascular and macrovascular complications [28, 29]. A recent meta-analysis of nine studies involving over one million people with type 1 diabetes or type 2 diabetes reported that depression was associated with a 38% increased risk of incident macrovascular disease and 33% increased risk of microvascular complications [29].

In one 10-year cohort study of individuals with childhood-onset diabetes, retinopathy severity was predicted by increasing duration of diabetes, with length of time spent in hyperglycaemia and with overall proportion of time depressed [50]. Similar results have been seen in people with type 2 diabetes; in one longitudinal study, those with high depression scores at both baseline and six-year follow-up were more likely to progress to diabetic retinopathy and to proliferative diabetic retinopathy than those with low depression scores [51].

One complication that may be particularly associated with depression is painful peripheral neuropathy. Recent studies suggest that not only is chronic pain a risk factor for depression, the presence of depression may itself worsen the experience of pain [52].

Depression, even if mild, is also associated with premature overall and cardiovascular mortality. A meta-analysis of 16 studies found that depression was associated with a 46% and 39% increased risk of all-cause and cardiovascular mortality, respectively [53]. In one study the annual mortality rate for those with diabetes and depression was 8%, 2.5-fold higher than those without either condition alone [54].

Management of people with diabetes and depression

The main aims of treatment are to reduce depressive symptoms and to improve self-care, glycaemic levels, and diabetes outcomes. A major difficulty for most clinics is the lack of readily available specialist mental health input, and this has been a disincentive for services to engage actively in tackling this important clinical problem [55]. By contrast, guidelines for the management of diabetes

now include support for psychological well-being [56, 57]. Most clinics should be able to provide first-response management for simple depressive disorders, although specialist help will still be required for more complex cases, where there is diagnostic uncertainty, lack of response to initial treatment, or suicide risk.

Screening and diagnosis of depression

The first step to the effective management of depression is its recognition and diagnosis. At present, screening and case finding are not part of the routine management of people with diabetes; however, given the high prevalence of comorbid depression in people with diabetes, this seems worthwhile and healthcare professionals should ensure they have appropriate skills to diagnose mood disorders.

A formal diagnosis of depression requires a time-consuming validated interview and so quick and cheaper screening methods are needed for primary and secondary care settings [58]. Although there are many short questionnaires that screen for depressive symptoms, it is important to use one that has been evaluated adequately in people with diabetes because of the overlap of symptoms between diabetes and depression, such as lethargy, irritability, or weight change [17]. Questionnaires that rely heavily on these symptoms tend to overestimate the likelihood of depression.

The most widely used and validated questionnaire in type 2 diabetes is the Patient Health Question-9 (PHQ-9) [59, 60]. It is also the shortest, containing nine questions, and can be easily completed by the person with diabetes alone. The cut-off for major depression is ≥10 points in primary care populations, but it has been suggested that use of a higher cut-off of ≥12 points in people with diabetes may improve the discrimination between diabetes-related symptoms and depressive symptoms [61]. Other well-validated questionnaires for people with diabetes include the Beck Depression Inventory, the Center for Epidemiologic Studies Depression Scale, and the Hospital Anxiety and Depression Scale (HADS) [51]. These questionnaires should not be used to diagnose depression, but rather to identify those who should undergo a diagnostic interview by a clinician.

Another straightforward approach that can be used by diabetes healthcare professionals is to ask two simple questions:

- During the past month, have you been bothered by having little interest or pleasure in doing things?
- During the past month, have you been bothered by feeling down, depressed, or hopeless?

If the answer to either is yes, the healthcare professional should ask if the person with diabetes want helps with this problem. If the answer to this is also yes, then the healthcare professional should undertake a diagnostic interview and offer appropriate referral and treatment.

While screening is a necessary first step, it alone is insufficient to improve clinical outcomes [58]. A Cochrane meta-analysis reported that depression screening in the general population had little or no impact on the detection and management of depression if used alone, and recommended that screening strategies could not be justified without organizational changes to ensure appropriate treatment if needed [62]. The importance of this for diabetes was demonstrated in a Dutch RCT that investigated the benefits of depression screening [63]. Following screening, although written feedback was provided to both participant and doctor, neither utilization of mental health services nor depression scores improved. Furthermore, without links to treatment, screening could lead to harm, including the stigma associated with depression, the risk of labelling transient distress as illness, and societal discrimination by insurance companies [49]. Several reasons might explain the observed low effectiveness of screening for depression in people with diabetes, including a low acceptance of screening and subsequent referral to further care by people with diabetes, failure to screen those at highest risk of depression, reluctance by healthcare professionals, and the generally poor quality of depression care in primary care systems [49].

Treatment of depression in people with diabetes

Knowledge of psychological interventions and appropriate drug therapy is important for diabetes healthcare professionals, as well as an awareness of the need for prompt referral to specialists when psychological difficulties continue to interfere significantly with well-being or diabetes self-management.

Previously people with diabetes were specifically excluded from trials of depression treatment and so consequently there were relatively few studies examining antidepressant and psychological treatment of depression in this population until recently. Nevertheless, more recent studies have clearly indicated that treating depression in diabetes with either psychological therapies or antidepressant medication is effective [64].

Psychological treatment

A variety of psychological treatments, including cognitive behavioural therapy (CBT), problem-solving, and psychodynamic techniques, have been used to treat depression in people with diabetes. These have been delivered in various settings in both primary and secondary care by different members of the healthcare team [64]. Others have used web-based and telephone contacts [65]. The trials have a preponderance of people with type 2 diabetes and no trials have been conducted with only people with type 1 diabetes. A meta-analysis of psychological treatments, including group-based and online therapies, reported they were effective for the treatment of depression with large effect sizes [64]. There is more debate about the effect on glycaemic levels [49], with one systematic review reporting a reduction in HbA_{1c} of ~0.6% (6 mmol/mol) [66] while another reported a less pronounced and overall non-significant improvement in glycaemic management (standardized mean differences [SMDs] from 0.40 to −1.40) [67]. Four trials on psychological interventions found improved glucose levels (SMD −0.25 to −0.68) [49]. The most recent systematic review found a small to moderate effect size (0.607; 95% CI 0.15 to 1.1) of psychotherapy interventions on glycaemic levels in people with depression and diabetes [64].

Pharmacotherapy

Effective and well-tolerated antidepressants are widely available and affordable and form an integral component of management for many people with depression. People with diabetes respond to antidepressants as well as the general population, with amelioration of depressive symptoms. Formal efficacy trials in people with diabetes are limited to a relatively small group of antidepressants, including nortriptyline, fluoxetine, bupropion, sertraline, paroxetine, and citalopram [49], leaving substantial gaps in the evidence for effectiveness (for both depression and glycaemic management) and safety for many commonly prescribed antidepressants. All antidepressants studied appear to have similar efficacy in terms of depression outcomes as long as adequate doses are used, with effect sizes of −0.61 SMD [67], but no trials have reported the medium- and long-term sustainability of pharmacological interventions for depression in diabetes after treatment cessation.

The treatment of choice depends largely on the side-effect profile, individual preference, and response. Selective serotonin reuptake inhibitors (SSRIs) are less cardiotoxic than tricyclic antidepressants, are safer in overdose, and consequently are widely used as first-choice agents. There are important drug–drug interactions with some members of this class and oral anti-diabetes agents through inhibition of the cytochrome P450 3A4 and 2C9 isoenzyme. For example, the use of fluoxetine may potentiate the effect of sulfonylureas, precipitating hypoglycaemia [68]. Some antidepressants, including mirtazapine, paroxetine, and some tricyclic antidepressants, may cause undesirable weight gain [41]. By contrast, bupropion, which is available in the USA, is associated with weight loss. Furthermore, unlike SSRIs, it does not appear to worsen sexual function and therefore may have advantages for people with diabetes [69]. Several new antidepressant medications have been approved, including vilazodone, vortioxetine, and levomilnacipran [70]. Differentiating these from most of those already available is a more benign weight gain profile for all three, fewer problems related to sexual functioning for vilazodone and vortioxetine, and potential relief of the cognitive dysfunction that can be associated with depression, as demonstrated with vortioxetine. None of these drugs, however, has been tested specifically in people with diabetes.

The clinical trials demonstrate a modest improvement in glycaemic levels with SSRIs (SMD −0.38) [49]. However, older studies have shown a mixed effect on glycaemic levels, ranging from hyperglycaemic effects with tricyclic antidepressant medications to euglycaemic or slightly hypoglycaemic effects with SSRIs and serotonin–noradrenaline reuptake inhibitors. Consequently, the findings of improved glycaemia with certain antidepressants should not be extrapolated to other untried antidepressants [49].

Most guidelines recommend that treatment should aim for complete remission of depressive symptoms. To achieve this, treatment must be sustained at an adequate dose for at least 4–6 months after remission has been attained to consolidate recovery and reduce the risk of relapse and recurrence. In addition to possible direct pharmacological effects, it should be remembered that treating depression may lead to a change in the individual's behaviour and routine, which may require adjustment of diabetes self-management. For example, if appetite improves, insulin requirements may increase, or if the person becomes more active, they may decrease.

Models of care

In most healthcare systems, depression is managed mostly within primary care and many diabetes healthcare professionals feel ill-equipped to manage depression. In the USA, a case management model known as *collaborative care* has been developed, whereby a multidisciplinary team works together to identify and treat depression within primary care settings. The model incorporates identification of high-risk cases, problem-solving therapy delivered by trained nurse case managers, and pharmacological treatments using a stepped-care approach. The first study to evaluate this approach was the Pathways study, which showed improvements in depression symptoms but no change in glycaemia [71]. Subsequently, greater attention was paid to intervention strategies for diabetes, resulting in improved glycaemic and blood pressure management as well as improved depressive symptoms [72]. In a meta-analysis of five studies from the USA, collaborative care was effective for treatment of depression, with a moderate effect size for depression outcomes and a small effect size for glycaemic levels [64]. As well as being clinically effective, these models of care are also highly cost-effective [73].

Anxiety disorders

The global prevalence of anxiety disorders in the general population is even higher than depression at 7.3%, and is continuing to increase in all regions of the world. Anxiety disorders are ranked as the sixth largest contributor to non-fatal health loss globally and appear in the top 10 causes of years lived with disability in all World Health Organization (WHO) regions [16]. Despite this high global burden, and the recognized stress associated with receiving a diagnosis of diabetes and then living with the condition, there has been relatively limited research on the relationship between anxiety and diabetes. Most studies have considered anxiety symptoms only as part of a depressive disorder, or have combined depressive and anxiety disorders in overarching terminologies of *common mental disorder* or *psychological symptoms*. There is, however, emerging evidence of an important bidirectional association between diabetes and anxiety disorders, related to adverse outcomes for both, independently of depression.

Case definition

Anxiety disorders comprise a group of mental disorders characterized by excessive worries or fears, somatic symptoms, and behavioural disturbances. Many of these symptoms and behaviours are commonly experienced in everyday life. However, in an anxiety *disorder*, they differ from *normal* experiences in terms of severity, course, and impact on functioning. The DSM-5 classification includes the following conditions under anxiety disorders [14]:

- Generalized anxiety disorder
- Panic disorder
- Separation anxiety disorder
- Selective mutism
- Specific phobia
- Social phobia
- Agoraphobia.

Previously, post-traumatic stress disorder (PTSD) and obsessive compulsive disorder were also included in this group. Although there are important differences in presentation, diagnostic criteria, epidemiology, and clinical management, specific anxiety disorders are often not differentiated in research, and at times even in clinical practice. By far the most common disorder is generalized anxiety disorder. DSM-5 diagnostic criteria for generalized anxiety disorder are given in Table 65.2 [14].

Epidemiology

Anxiety disorders are the most common of all mental disorders, and affect almost 30% of the adult population at some point in their life [74]. As is the case for depression, anxiety disorders are more common in women than men, and are associated with lower socioeconomic status and chronic diseases. All age groups can be affected, with a trend towards a lower prevalence in older age groups. Anxiety disorders contribute a considerable burden of disease; in 2016, they were responsible for 357 disability-adjusted life years lost per 100 000 globally, second only to depression [75].

Most studies of anxiety and diabetes have been conducted in clinical, typically hospital, settings rather than in community populations. Studies have often not distinguished between the various types of anxiety disorders, or even between anxiety *symptoms* and anxiety *disorder*. Where specific disorders have been investigated,

Table 65.2 DSM-5 diagnostic criteria for generalized anxiety disorder.

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).
B. The individual finds it difficult to control the worry.
c. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months):
   Note: Only one item required in children.
   1. Restlessness, feeling keyed up or on edge.
   2. Being easily fatigued.
   3. Difficulty concentrating or mind going blank.
   4. Irritability.
   5. Muscle tension.
   6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).
D. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
E. The disturbance is not attributable to the physiological effects of a substance (e.g. a drug of abuse, a medication) or another medical condition (e.g. hyperthyroidism).
F. The disturbance is not better explained by another medical disorder (e.g. anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive–compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).

Source: American Psychiatric Association 2013 [14].

studies have mostly reported on generalized anxiety disorder and PTSD. A further limitation of research in this area is that, unlike for depression, scales used to detect and measure anxiety have not been validated in diabetes populations. This is an important consideration, since a key challenge in diabetes is distinguishing between symptoms of anxiety and symptoms associated with hypoglycaemia. Symptoms common to both include adrenergic (e.g. tachycardia, sweating, pallor), mood, and cognitive disturbances. The presence of these symptoms in the absence of hypoglycaemia (or hyperglycaemia) would indicate that they are driven by anxiety.

Another challenge is distinguishing between an anxiety disorder and the understandable distress and fears commonly associated with living with and managing diabetes. A number of scales have been developed to assess diabetes-specific anxieties. The Hypoglycaemia Fear Survey [76] and the Fear of Complications Questionnaire [77] measure fears among people with type 1 diabetes. There is also the common fear of various invasive procedures (injecting insulin, blood glucose testing), which can be assessed using the Diabetes Fear of Injecting and Self-Testing Questionnaire [78] and the Measure of Invasiveness and Skipping Self-Monitoring [79].

The gold standard for making a diagnosis of an anxiety disorder is clinical interview, using recognized diagnostic criteria. The most common instruments used in research are the Beck Anxiety Inventory [80], the Hospital and Anxiety Depression Scale (HADS) [81], and the Generalized Anxiety Disorder Scale-7 (GAD-7) [82]. Despite its name suggesting otherwise, the GAD-7 does not only detect generalized anxiety disorder, but also panic disorder, social anxiety disorder, and PTSD [83]. It cannot, however, be used to distinguish between these conditions. Although none of these instruments has been validated for use in diabetes, they are widely used in practice to screen or assess anxiety in chronic conditions.

A systematic review of 18 studies including 2584 adults with diabetes reported that generalized anxiety disorder was the most common type of disorder, with a current prevalence of 13.5% and lifetime prevalence of 20.5% [84]. Current and lifetime prevalences for panic disorder and PTSD were much lower (1.3% and 1.9%; and 1.2% and 3.7%, respectively). The prevalence of elevated symptoms of anxiety was 40%, higher in women than men, but similar for both type 1 diabetes and type 2 diabetes. A later meta-analysis of 12 studies with 12 626 people with diabetes reported a 25% increased risk of having an anxiety disorder or anxiety symptoms in people with diabetes compared to those without diabetes. The risk was increased by 20% for anxiety disorder (seven studies) and by 48% for anxiety symptoms (five studies) [85].

There have been wide variations in prevalence of anxiety reported across countries, which may be due to differing approaches to case ascertainment, heterogeneous study populations, and inconsistent distinction between anxiety disorders and symptoms. A recent study used the Mini-International Neuropsychiatric Interview to diagnose anxiety in 3170 adults with type 2 diabetes attending outpatient clinics in 15 countries [86]. The overall prevalence of anxiety disorders was 18%; 8.5% had generalized anxiety disorder and 5.1% had a lifetime diagnosis of panic disorder. Despite using a standardized approach for case ascertainment, there was huge variation in prevalence estimates between countries, ranging from 0% in Bangladesh to 72% in Ukraine. The authors suggest these differences may be driven in part by cultural differences in presentation and reporting of symptoms.

There have been a few longitudinal studies investigating the incidence of diabetes in anxiety and vice versa. A systematic review and meta-analysis of 15 studies and ~1.8 million participants reported that incident diabetes was increased by ~50% in those with baseline anxiety, confirming that both anxiety symptoms and anxiety disorders are risk factors for diabetes [87]. PTSD was also associated with an increased diabetes risk (OR 1.5; 95% CI 1.1 to 2.1). The review included only two studies of the incidence of anxiety in people with diabetes (one in a multiple sclerosis population), both showing no association [88, 89]. However, significant methodological limitations of these studies preclude any definitive conclusions. Several other studies, not eligible for this review, have indicated that diabetes is likely a risk factor for anxiety. For example, a study using data for around one million people from a Taiwanese insurance database reported a higher annual incidence of anxiety disorder over five years in people with diabetes [90]. Further research is needed to better understand this relationship.

Studies in children and adolescents have also shown an association between diabetes and anxiety, with one study reporting a 2.5-fold increased risk of developing incident anxiety over 26 years in young people with type 1 diabetes [91]. A systematic review of symptoms of depression and anxiety in young people with type 1 diabetes found 13.4% and 17% of participants with state and trait anxiety scores, respectively [92]. A recent systematic review of anxiety in children and adolescents with chronic conditions, including three studies with 336 young people with type 1 diabetes, reported prevalence ranging from 15.5% to 32.1% compared with 0% to 8% in the control groups [93].

Who is likely to develop an anxiety disorder?

The risk factors for developing an anxiety disorder in the general population are also relevant in diabetes, with women, younger people, and those with chronic medical conditions at highest risk [85, 86, 94, 95]. Depression is also a risk factor for anxiety, although the latter disorder is often overlooked in the presence of depressive symptoms. Factors specific to diabetes include longer duration of diabetes, fear of hypoglycaemia, and insulin use. The risk of an anxiety disorder, however, seems to be similar for type 1 diabetes and type 2 diabetes [87].

In one study of people with type 1 diabetes, 25% of participants met criteria for PTSD using self-reported symptoms, with PTSD related to hypoglycaemia [96]. In another study, 9% of people with diabetes using insulin reported anxiety symptoms related to self-administration of insulin [97], while an earlier study reported that 28% of people using insulin experienced anxiety related to self-injection [98].

Anxiety disorders as a risk factor for diabetes

Anxiety disorders are associated with an increased risk of diabetes [87]. Although this association may in part be mediated by the coexistence of depression, there is emerging evidence that anxiety is an independent predictor of incident diabetes. In 2156 adults initially free of diabetes, a positive anxiety screen predicted a diabetes diagnosis over a 10-year follow-up period [99]. The evidence for an association is strongest for PTSD, with several prospective studies reporting that PTSD increases odds of incident diabetes during follow-up (OR ranging from 1.3 to 2.1) [100–102].

Proposed mechanisms linking anxiety and diabetes

Although direct evidence is limited, several plausible biological and psychological mechanisms may help explain the link between anxiety and diabetes.

Biological mechanisms

Several biological pathways may mediate this association; one possible mechanism is via the HPA axis [103]. Anxiety may initiate activation of the HPA axis, triggering release of counter-regulatory hormones, such as glucagon, adrenaline, noradrenaline, cortisol, and growth hormone. Cortisol also stimulates the sympathetic nervous system, which is associated with symptoms of anxiety. Chronic anxiety may lead to insulin resistance, visceral adiposity, dyslipidaemia, and hypertension and an increased risk of type 2 diabetes [104, 105].

A related proposed mechanism to explain the relationship between anxiety and diabetes, which also implicates the HPA axis, is the concept of allostasis [106]. This refers to the dynamic process of adaptation to environmental challenges via changes in multiple biological pathways, including the HPA axis, autonomic nervous system, and metabolic and immune systems. The purpose of these adjustments is to maintain homeostasis, but sustained stimulation may lead to *allostatic load*, which manifests as chemical imbalances, changes in diurnal rhythm of hormones, and even atrophy of brain structures. A study of allostatic load compared people with type 2 diabetes with matched people without diabetes; post-stress recovery in blood pressure, heart rate, and cholesterol were impaired in the group with diabetes [107]. Among other changes, cortisol and interleukin (IL)-6 concentrations were elevated, while people with diabetes reported greater stress experience than those without diabetes.

Studies in PTSD-discordant twins lend support to these putative mechanisms and suggest common biological and behavioural factors for both PTSD and diabetes [102]. PTSD is often associated with disruption of HPA axis regulation and the other mechanisms already described [108, 109]. However, the evidence is by no means unequivocal, as no consistent pattern of HPA alteration has been found [109]. PTSD is also associated with chronic hyperarousal of the sympathetic nervous system and renin–angiotensin–aldosterone system, which in turn is associated with neurometabolic changes, inflammation, and oxidative stress [110]. PTSD has been associated too with abnormalities in limbic-neuronal structure and function that contribute to central regulation of body weight.

Psychological mechanisms

People with diabetes may experience heightened anxiety related to many aspects of diabetes. Receiving a diagnosis of diabetes is often viewed as life-changing, bringing with it anxieties about undesirable changes to lifestyles, and fears of complications and even of shortened life expectancy [95, 103]. There may also be anxieties related to treatment, particularly with insulin, including fear of hypoglycaemia, glucose self-monitoring, and self-administration of insulin. Around 60% people with diabetes report anxiety about managing their type 2 diabetes; and this anxiety is associated with less effective self-management, persistent hyperglycaemia, and higher levels of diabetes complications.

Additionally, in common with other chronic disorders, the demands of self-care and increased need to access healthcare can be stressful and may have a significant impact on day-to-day life activities, including employment. Diabetes may be associated with adverse economic consequences by affecting earnings and employment, particularly in the presence of diabetes complications, contributing a further source of stress [111]. These multiple stressors are likely to mediate the increased risk of anxiety disorders seen in diabetes [95].

Consequences of anxiety in diabetes

Although it might be anticipated that anxiety would improve motivation to carry out self-management behaviours, and therefore lead to better glycaemic management, the evidence on outcomes of comorbid diabetes and anxiety disorders is mixed. A systematic review and meta-analysis of 12 studies found anxiety was not associated with glycaemic levels, but when limiting the analysis to studies using diagnostic interviews anxiety was associated with hyperglycaemia [112]. Several later studies have reported stress and anxiety to be associated with less effective diabetes self-management [113–116]. High levels of self-reported anxiety have also been associated with poor perceived glycaemic management, a greater number of diabetes complications, and poorer quality of life [117, 118]. In a recent multicountry study, presence of generalized anxiety disorder and current panic disorder as well as lifetime panic disorder were all significantly associated with persistent hyperglycaemia [86], but this was not replicated in another study from Portugal [119]. The discrepant results may be explained by a number of methodological limitations, including conflating anxiety symptoms with anxiety disorder, use of self-report measures for case finding, and cross-sectional design. A longitudinal study from the Fremantle Diabetes Study Phase II found no direct effect of generalized anxiety disorder on BMI, HbA_{1c}, smoking status, and blood glucose self-monitoring, although lifetime anxiety disorder was independently associated with increased risk of subsequent severity of depressive symptoms [120]. A four-year follow-up to this study found that a significant proportion

of individuals (13%) continued to report elevated anxiety symptoms, but they were not associated with health-related outcomes over time [121]. Another longitudinal study reported a ~20% increased mortality risk in men with diabetes in the presence of anxiety symptoms, but not in women [122].

In children and young people with diabetes, a systematic review identified eight studies (six cross-sectional and two longitudinal) investigating the association between anxiety and disease management and glycaemia [93]. Again, there were mixed findings: three studies reported an association between higher anxiety and suboptimal diabetes management; one study found no association; and one found a relationship between high anxiety scores and both reduced HbA_{1c} and improved medication taking. A study investigating the association between social anxiety and diabetes-related outcomes found a positive association with self-reported moderately prudent (as opposed to either poor or good) diet, and with restricted food and drink intake.

In summary, there is inconsistent and contradictory evidence of an association between anxiety, self-management behaviours, glycaemia, and adverse outcomes in diabetes.

Management of people with diabetes and anxiety disorders

Although evidence for the effects of coexisting anxiety and diabetes on outcomes is equivocal, it is nevertheless clear that this comorbidity places a considerable burden on a significant proportion of people with diabetes. However, evidence-based guidance on the detection and management of anxiety disorders in diabetes is limited, often addressing anxiety symptoms only in the context of depression. The National Institute for Health and Care Excellence (NICE) guidelines on the management of type 2 diabetes [123], for example, do not mention anxiety disorders, and the Canadian Diabetes Association Clinical Practice Guidelines combine recommendations for depression and anxiety [124].

Screening and diagnosis of anxiety disorders

Recognition and diagnosis of anxiety in diabetes are a critical first step for effective management. Although there has been no evaluation of routine screening for anxiety in people with diabetes (and future research should address this evidence gap), given the considerable evidence that it is prevalent, persistent, and distressing, and the availability of effective treatments, regular screening for anxiety is recommended. The American Diabetes Association Position Statement recommends screening at diagnosis, at periodic intervals, and when there is a change in disease, treatment, or life circumstance; including caregivers and family members in this assessment is recommended [56].

When assessing for anxiety in diabetes, care needs to be taken to distinguish symptoms of anxiety from those of hypoglycaemia. Monitoring blood glucose while symptomatic can help make the distinction. Screening and diagnostic measures for anxiety have not been validated specifically in people with diabetes, while the gold standard is a clinical diagnostic interview conducted by a trained clinician. This may not be practicable in non-mental health settings. Screening tools such as GAD-7 [83] and HADS [81] can be used by non-specialists, with onward referral for confirmation of diagnosis and treatment as needed.

Treatment of anxiety in people with diabetes

Knowledge of treatment options and services for anxiety is important for healthcare professionals working in diabetes services. Although evidence for effective treatments specifically in diabetes is sparse, there is a well-established evidence base for the management of anxiety disorders in the general population.

Psychological treatment

Psychological treatments either alone or in combination with pharmacotherapy, using a stepped care approach, are the mainstay in the management of anxiety disorders. Early identification and communication of the diagnosis, with psychoeducation, are the first steps, and may be sufficient to help alleviate mild symptoms of anxiety without further intervention. A range of low-intensity psychological interventions, including self-help resources, guided self-help, or psychoeducational groups, are the first-line management for those with ongoing symptoms following a period of monitoring. For those with marked functional impairment, or not responsive to low-intensity treatments, individual high-intensity psychotherapy (CBT) should be offered [125].

Trials of psychological therapies in people with diabetes have typically not targeted anxiety disorders, but rather symptoms of anxiety either as part of a depressive disorder or undifferentiated *common mental disorder*. A systematic review of the effectiveness of CBT on glycaemic levels and psychological outcomes in adults with diabetes identified 4 studies examining anxiety as an outcome and 11 measuring HbA_{1c} [126]. CBT was effective for reduction of anxiety symptoms at 3 and 6 months but not at 12 months, and for a significant short- and medium-term reduction in HbA_{1c}. These studies did not target individuals with a diagnosed anxiety disorder or elevated anxiety symptoms.

Pharmacotherapy

Effective pharmacological treatments for anxiety include SSRIs and tricyclic antidepressants [127]. These may be used instead of, or in combination with, psychotherapy in people with significant anxiety symptoms, depending on individual preference [125]. They should be reserved for individuals who have not responded to low-intensity interventions, or who have debilitating symptoms with significant functional impairment. As these drugs may affect glycaemic levels, closer blood glucose monitoring is recommended.

Models of care

There is a need for healthcare professionals with specific training in the detection and management of anxiety disorders working within diabetes services. Studies have shown that people are more likely to follow through and access mental healthcare that is co-located [128]. Few healthcare systems have mental health expertise embedded within physical health services and resource constraints limit the wider roll-out of such models of care. Collaborative care models [129], which have been found to be effective for the management of depression and diabetes, could also offer a feasible approach for delivering evidence-based management of anxiety in primary care or diabetes services [103].

Eating disorders

Eating disorders are the second most common mental illness in people with type 1 diabetes [95]. Eating disorders and disordered eating in diabetes encompass a broad spectrum of conditions, ranging from well-defined eating disorders like anorexia or bulimia nervosa to harmful diabetes self-care behaviours driven by fear of weight gain, with direct and indirect insulin restriction being the most common [130]. People with type 1 diabetes and

eating disorders have described their dual condition as a vicious cycle between having diabetes and disordered eating cognitions reinforcing each other [131, 132].

Because eating disorders are commonest in adolescents and young adults, there has been more research on the co-occurrence of eating disorders and type 1 diabetes [133]; far less is known about such problems in the larger population with type 2 diabetes [134–138]. Nevertheless, binge eating disorder and bulimia nervosa are seen as risk factors for type 2 diabetes and are associated with insulin resistance [139, 140].

Comorbid eating disorders significantly increase mortality [141, 142] and incidence of acute [143, 144] and late diabetes complications [145–147]. Currently, there is no evidence-based treatment that also improves glycaemia-related clinical outcomes [148].

Case definitions

The DSM-5 [14] and WHO International Classification of Diseases, 11th edition (ICD-11) [149] define three common eating disorders:

- Anorexia nervosa
- Bulimia nervosa
- Binge eating disorder.

Neither publication, however, acknowledges the specifics of eating disorders as a comorbidity to diabetes; in particular, there is no consideration of the relation to acute metabolic complications such as diabetic ketoacidosis, and chronic microvascular or macrovascular complications, as well as diabetes-specific cognitions such as the fear of insulin as promoting weight gain and behaviours including insulin restriction.

Clinicians with experience of working with people with diabetes and eating disorders have voiced the need for clarity in definition and for clinical diagnostic criteria for the spectrum of this dual condition. The coexistence of the two disorders goes beyond the current definition of *classical eating disorder*, because a large proportion of presenting clinical cases do not fit the established categories of eating disorders in spite of their significant clinical risk [150]. There is currently no clear international consensus on the definition of the wider spectrum of disordered eating in type 1 diabetes that accounts for the unique feature of insulin omission or restriction to control or reduce weight. This is an area of intense clinical research [151], with new clinical definitions emerging, such as *type 1 diabetes with disordered eating* (T1DE) and *diabulimia* [131, 134, 150]. However, these terms have not yet been included in the diagnostic catalogues.

With the exception of the Diabetes Eating Problem Survey-Revised (DEPS-R) [152] and the modified Sick, Control, One, Fat, Food tool (mSCOFF) [153], commonly used eating disorder or disordered eating self-report questionnaires, diagnostic interviews, and diagnostic criteria do not include questions on diabetes-specific disordered eating cognitions or diabetes self-care behaviours arising from these, nor are they validated for people with type 1 diabetes.

Eating disorders exist on a continuum of severity, and there is a lack of good evidence on which to establish a formal boundary or cut-off for *clinical* significance. When an eating disorder co-occurs with a chronic condition such as diabetes, its significance is increased by the potential for harm resulting from impaired self-care and acute and chronic hyperglycaemia. Thus eating disorders, which may be seen as *mild* in an otherwise healthy individual, may be moderate to severe in terms of risk for adverse clinical outcomes in a person with diabetes. The clinical red flags for severity in people with diabetes are persistently high HbA_{1c} (>86 mmol/mol, 10%), and recurrent hospital admissions in hyperglycaemia or diabetes ketoacidosis or with severe hypoglycaemia.

Table 65.3 DSM-5 diagnostic criteria for anorexia nervosa, bulimia nervosa, and binge eating disorder, and clinical features of type 1 diabetes disordered eating (T1DE).

Anorexia nervosa
- Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected.
- Intense fear of gaining weight or becoming fat, even though underweight.
- Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.

Bulimia nervosa
- Recurrent episodes of binge eating. An episode of binge eating is characterized by (1) eating, in a discrete period of time (e.g. within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances; and (2) a sense of lack of control over eating during the episode.
- Recurrent inappropriate compensatory behaviour to prevent weight gain, such as: self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting or excessive exercise.
- The binge eating and inappropriate compensatory behaviours both occur, on average, at least once a week for 3 months.
- Self-evaluation is unduly influenced by body shape and weight.
- The disturbance does not occur exclusively during episodes of anorexia nervosa.

Binge eating disorder
- Recurrent episodes of binge eating. An episode of binge eating is characterized by (1) eating, in a discrete period of time (e.g. within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances; and (2) a sense of lack of control over eating during the episode.
- The binge eating episodes are associated with three (or more) of the following: (1) Eating much more rapidly than normal. (2) Eating until feeling uncomfortably full. (3) Eating large amounts of food when not feeling physically hungry. (4) Eating alone because of feeling embarrassed by how much one is eating. (5) Feeling disgusted with oneself, depressed, or very guilty afterward.
- Marked distress regarding binge eating is present.
- The binge eating occurs, on average, at least once a week for 3 months.
- The binge eating is not associated with the recurrent use of inappropriate compensatory behaviour as in bulimia nervosa and does not occur exclusively during the course of bulimia nervosa or anorexia nervosa.

T1DE (type 1 diabetes disordered eating) and diabulimia (not part of DSM-5 criteria)
- Established diagnosis of type 1 diabetes.
- Restriction or omission of insulin with the intention to control body weight.
- Persisting hyperglycaemia, or problematic hyperglycaemia and/or high glycaemic variability.
- Recurrent admissions in diabetic ketoacidosis; recurrent problematic hypoglycaemia.

Source: American Psychiatric Association 2013 [14].

The diagnostic criteria for the common forms of eating disorder and clinical features of TIDE are given in Table 65.3.

Epidemiology

Binge eating disorder is the commonest eating disorder, with an estimated lifetime prevalence of 2.6% among US adults, more than the prevalence for bulimia nervosa and anorexia nervosa

combined, with a gender ratio that is far less skewed [154, 155]. In contrast, ~1 in 250 females and 1 in 1000 males will experience anorexia nervosa, usually during adolescence or early adult life. Bulimia nervosa is more common, affecting 0.5–1% of young women in community studies. Longitudinal studies have shown that eating disorder diagnoses are often unstable over time, and cross-sectional studies underestimate the proportion of the population affected in the long term. Incidence rates in adolescent and young adults are higher than previously estimated.

Eating disorders are twice as common in people with type 1 diabetes than in the general population [156], with prevalence rates ranging between 0.9% in clinical databases [144], to 27% in females and 8.6% in males in population-based studies [157] and up to 36% in screening studies [158–160], depending on age group, gender, and case definition. This reflects the poor classification of the spectrum of T1DE, resulting in these broad prevalence estimates and possibly a high number of cases remain undetected. Insulin restriction in type 1 diabetes, which is seen to varying degrees in eating disorders, is associated with threefold increased mortality compared to those who do not restrict insulin [146]. Intentional insulin omission occurs remarkably frequently, increasing from 2% among girls aged 9–13 years, to 11% among girls aged 12–19 years, to 34–40% among young women aged 16–30 years [161]. Mortality is driven by accelerated onset of late diabetes complications secondary to persistent hyperglycaemia [146, 162] and by acute metabolic complications due to insulin omission or overdose.

For type 2 diabetes the epidemiological data are even scarcer, with prevalence estimates for binge eating disorder ranging from 1.4% to 29% and night eating syndrome 3.8% [133, 135, 163].

Diabetes as a risk factor for the development of an eating disorder

The diagnosis of diabetes can trigger the onset of an eating disorder in a person with pre-existing vulnerability factors, like early life events, important transitions, past psychiatric history, or personality factors (perfectionism). For example, for someone putting body weight and image at the centre of their self-evaluation, the experience of drastic weight loss in the run-up to the diagnosis of type 1 diabetes with following weight regain due to rehydration and re-insulinization, as well as the focus on carbohydrate content and food intake mandated by diabetes self-management, may drive the development of an eating disorder [132]. Predisposing traits of perfectionism, low self- and body esteem, and interpersonal and emotion regulation difficulties [158, 164] increase vulnerability to disordered eating in those with type 1 diabetes, once they interact with the necessary focus on eating in type 1 diabetes, a mechanism also discussed in an earlier conceptualization of type 1 diabetes and disordered eating [141]. This provokes unhelpful behaviours, such as strict dieting, restricting insulin, and binge eating, leading to neuroadaptive changes driven by of loss of control over eating and fluctuations in plasma glucose [165]. Maintenance cycles of sustained disordered eating behaviour involve dietary restriction leading to hypoglycaemia, binge eating and hyperglycaemia, and purging or insulin restriction [132, 166].

In addition, interpersonal conflicts with carers or peers around what should or should not be eaten can perpetuate the problem, as described in recent transdiagnostic and cognitive behavioural theoretical models [132, 165, 166]. For example, the thoughts and cognitions driving insulin restriction behaviour range from fear of weight gain, fear of hypoglycaemia (because of adverse past experience or due to high hypoglycaemia symptom threshold), feeling of control through manipulating insulin, to feeling of emotional numbness at marked hyperglycaemia [131, 132].

Aetiology

The causes of eating disorders are incompletely understood, but dieting appears to be an important risk factor, although only a small proportion of all those who diet go on to develop a disorder. Other known risk factors include female sex, early puberty, a history of obesity or gaining weight, peer and cultural influences, and certain personality traits including perfectionism and low self-esteem. Family relationships are often disturbed, although this may be either a cause or consequence of the disorder, or both.

Several of these factors may be magnified by the demands of the diagnosis or management of diabetes. People with type 1 diabetes have to match their insulin injections to carbohydrate intake, exercise, illness, and glucose levels, which involves a relentless self-care routine that puts a focus on food and self-management. People with type 2 diabetes are encouraged to make lifestyle changes, including dietary changes with reduction of high-calorie fatty and sugary foods, and increased exercise while aiming for weight reduction. This can lead to a preoccupation with food and body weight. Instead of relying on physiological cues related to hunger and satiety, food intake is brought under cognitive control, which can lead to feelings of low self-esteem and mood if self-imposed targets are missed. This in turn may drive further dietary restraint with a greater likelihood of subsequent failure, thereby causing a vicious cycle.

On average, people with type 1 diabetes are heavier than their peers and this may trigger dieting, weight preoccupation, and altered body image perception. Furthermore, there is a conflict between optimal glycaemia and body weight, as weight tends to increase as HbA_{1c} comes down [167]. Insulin treatment can lead to weight gain due to insulin's anabolic properties and the need for hypoglycaemia to be treated with additional carbohydrates. The pronounced weight fluctuation at diagnosis of type 1 diabetes can be very unsettling and reinforce eating disorder cognitions [132]. People with diabulimia have reported self-experimenting with insulin omission, considering insulin as their secret tool for weight loss, and also the empowerment through the insulin restriction being the one element of their diabetes self-care they can control [131].

In contrast, there may also be protective factors, for example self-compassion, resilience, aiming for 'good enough' diabetes management (not perfection), acceptance of diabetes as part of, but not defining, their identity, and prioritizing health over weight concerns [132].

Impact on diabetes outcomes

Eating disorders, especially if persistent, are a major cause of poor outcome in people with diabetes [145]. In the short term severe hypoglycaemia, diabetic ketoacidosis, and hospital admission are all more common in those with eating disorders [144, 168]. Rates of serious micro- and macrovascular complications and mortality are significantly increased, even if the eating disorder is relatively short-lived. However, the incidence of long-term complications increases with the duration of insulin omission. In one study, 86% of females with type 1 diabetes and severe eating disorders developed retinopathy after four years compared to 24% of those without eating disorders [147]. In a 10-year follow-up study of females with type 1 diabetes, a quarter of those who reported insulin omission had nephropathy, compared with 10% of those who did not [146].

Mortality rates in females with type 1 diabetes are increased ~16-fold in those with an eating disorder compared to those with diabetes alone (34.6 vs 2.2 per 1000 person-years) [142].

Clinical features

Anorexia nervosa

The hallmark of anorexia nervosa is weight loss, usually achieved by a combination of extreme dieting, exercise, and, less commonly, self-induced vomiting. Misuse of laxatives and other weight-reducing substances (e.g. diuretics, thyroxine) may also occur. In addition to these features, people with type 1 diabetes may resort to insulin omission as a purging mechanism, whereby rapid body weight loss can occur, associated with dangerous acute metabolic complications such as diabetic ketoacidosis, dehydration, and electrolyte disturbances.

People with anorexia nervosa experience a characteristic set of attitudes and values concerning body shape and weight, which include intense feelings of fatness and extreme fear of loss of control over eating and consequent weight gain. Their body image is distorted and they express a level of dissatisfaction with their shape and weight, which is far beyond that seen in the general population. There is a tendency to judge their self-worth almost solely in terms of weight, shape, and ability to control food intake.

Anorexia nervosa usually begins in adolescence, although prepubertal and adult onset may occur. For some the natural body changes of adolescence appear to be a risk factor; weight loss associated with a diagnosis of type 1 diabetes and then commencement of insulin treatment and subsequent weight gain may therefore act as a trigger [132].

The low weight of people with anorexia nervosa gives rise to the physiological and psychological features of starvation, including ritualized eating habits, cognitive rumination about eating, irritability, poor concentration, constant feelings of cold and misery, and decreased activity. Social withdrawal and isolation are common, and anxiety, obsessional features, and suicidal thoughts sometimes occur. 'Fattening' foods are typically avoided and the diet contains an average daily intake of calories in the region of 600–900 kcal/d, with very low fat and mineral intake. Most people with anorexia continue to feel hungry, and as such the term anorexia is a misnomer. The effects on hunger and appetite of persistent hyperglycaemia combined with insulin deficiency and ketosis in people with type 1 diabetes remain controversial. Some report paradoxical craving for sweet drinks, whereas others lose their appetite completely.

Common physical symptoms include gastrointestinal complaints (constipation, fullness after eating, bloating, and abdominal pain), lack of energy, reduced libido, early waking, and postural dizziness. Amenorrhoea is often present, with infertility and osteopaenia being significant risks. Those with prepubertal onset are often small in stature and show failure of breast development. Bradycardia, hypotension, and peripheral neuropathy are also reported, and a range of endocrine abnormalities may be found, including low sex hormone and tri-iodothyronine levels (with normal thyroxine and thyroid-stimulating hormone [TSH]), and raised growth hormone and cortisol. Autonomic and peripheral neuropathy are common in people with diabetes and anorexia nervosa, as the combination of starvation, extreme glycaemic variability [169], too rapid improvement of glycaemia during treatment, and long-term hyperglycaemia drastically increases the risk of microvascular complications [170].

People with type 1 diabetes can often be clinically severely ill at a BMI range that in conventional eating disorders care might not yet meet the threshold for inpatient admission. This is due to the additional physical health risks arising from the combination of type 1 diabetes, starvation, and insulin restriction. The risk of severe hypoglycaemia is high, due to lack of glycogen storage for counter-regulation and reluctance to take hypoglycaemia treatment that is perceived as extra calories. The risk for severe electrolyte disturbances from fluctuating insulin and glucose levels, dehydration, and inappropriate rehydration, as well as the risk for diabetic ketoacidosis are high. Overexercising and carbohydrate and calorie restriction are dangerous for a person with type 1 diabetes as these increase the risk of severe hypoglycaemia.

Bulimia nervosa

Bulimia nervosa is characterized by recurrent episodes of binge eating in which large amounts of food are consumed (typically ≥2000 kcal) during which the individual feels unable to control the eating. This behaviour is accompanied by a range of *compensatory* behaviours designed to prevent weight gain, including dietary restriction, vomiting, exercise, and laxative or diuretic misuse. Insulin restriction and omission (primarily in people with type 1 diabetes) and/or withholding other glucose-lowering agents are often used as compensatory or purging behaviour in bulimia nervosa.

People with bulimia nervosa have broadly the same set of attitudes and beliefs to those seen in anorexia nervosa. Although most individuals fall within the normal weight range, some have a history of underweight and may have previously met the diagnostic criteria for anorexia nervosa, while others are overweight. The vicious cycle of dieting, bingeing, purging, and fear of weight gain invariably has a detrimental impact on other aspects of functioning, such as work and social relationships, and can have financial implications resulting from the cost of the food. For some, binge eating seems to serve an important function by regulating unpleasant emotional states. Others have different impulse control problems and a history of interpersonal difficulties. Depression and self-harming behaviours such as cutting, overdosing, or substance misuse may occur; insulin omission can be considered as a form of self-harm. For a person with diabetes, hypoglycaemia can be an important trigger for binge eating episodes and vice versa [132, 169].

Physical complications of bulimia nervosa include enlargement of the parotid glands, erosion of dental enamel, and hypokalaemia from vomiting or laxative or diuretic misuse. With comorbid diabetes, the electrolyte and fluid imbalance can be more pronounced and dangerous, due to the large fluctuations of glucose and insulin causing osmotic and electrolyte shifts between intra- and extracellular compartments. Vomiting and overexercising increase the risk of severe hypoglycaemia. Vomiting may also have adverse effects on pre-existing diabetic retinopathy. Insulin restriction and omission can cause rapid dehydration and diabetic ketoacidosis.

Binge eating disorder

Binge eating disorder is defined by recurrent episodes of binge eating (eating in a discrete period of time an amount of food larger than most people would eat in a similar amount of time under similar circumstances and a sense of lack of control over eating during the episode), occurring on average at least once a week for three months, and associated with marked distress [14]. Binge episodes are also associated with ≥3 of the following:

- Eating rapidly.
- Eating until feeling uncomfortably full.

- Eating large amounts of food when not feeling physically hungry.
- Eating alone because of feeling embarrassed by how much one is eating.
- Feeling disgusted with oneself, depressed, or guilty afterwards.

Unlike those with bulimia nervosa, persons with binge eating disorder do not regularly engage in compensatory behaviours. Although many people with binge eating disorder have obesity, more than half have a BMI <30 kg/m^2, including 19% whose weight is normal [155].

The cognitions driving binge eating disorder can impact diabetes self-care and vice versa in a vicious cycle. For example, the feeling of guilt after a binge eating episode can increase the fear of diabetes complications, which then leads to the impulse of giving too much short-acting insulin to correct the hyperglycaemia following a binge eating episode, thus driving hypoglycaemia, which then may trigger the next binge eating episode [169].

Type 1 diabetes and disordered eating and diabulimia

Although the development and refinement of clinical criteria for these conditions are currently a work in progress, we have included the terms T1DE and diabulimia here as they are increasingly used by health professionals, people with diabetes, and researchers to describe disordered eating in type 1 diabetes [131, 150]. The key feature in the definition of T1DE or diabulimia is the pervasive fear of insulin as weight gaining leading to direct insulin restriction (complete insulin omission with the intention of losing weight) or indirect insulin avoidance through food restriction. Clinical severity indicators include very low BMI (below 15 kg/m^2), HbA_{1c} consistently above 86 mmol/mol (10%) for more than 12 months, more than one admission in diabetic ketoacidosis in the past two years, and one or more severe hypoglycaemic episodes in the past year.

There will be significant overlaps between the classical eating disorders and the wider spectrum of T1DE and further research is under way to develop subtype classifications and clinical diagnostic and screening tools.

Management of eating disorders

Detection

Although some people with diabetes may volunteer information about eating problems or insulin restriction to control their body weight, many will be secretive as a result of factors including denial, guilt, or shame [131]. Thus an essential first step in management is successful detection of the problem. It is important to note that although eating disorders are generally associated with poor self-care and erratic glycaemic levels, alternating periods of hypo- and hyperglycaemia may be undetected by HbA_{1c}, although they may be uncovered with continuous glucose measurement [169]. Warning symptoms include:

- Marked weight fluctuation or loss.
- Symptoms of hyperglycaemia (thirst or tiredness).
- Persistently increased HbA_{1c}.
- Marked glycaemic variability.
- Frequent episodes of ketoacidosis (often requiring hospital admission) or severe hypoglycaemia leading to loss of consciousness, seizures, or needing third-party assistance.
- Growth retardation and pubertal delay in younger people with type 1 diabetes.

Most of these features are not specific for eating disorders and are only indicative of poor diabetes self-care. The only way to establish a diagnosis of an eating disorder is by a clinical interview, although brief self-report scales may be a useful means of screening.

General diagnostic questionnaires for detecting eating disorders are inappropriate for individuals with type 1 diabetes, as they do not identify features that are unique to type 1 diabetes, such as insulin omission. Furthermore, some aspects of normal diabetes management may be viewed as disturbed eating in the general population. DEPS-R is a 16-item diabetes-specific self-report measure of disordered eating that was designed specifically for people with diabetes [152], while the mSCOFF questionnaire is a simple five-item screening to be used by diabetes healthcare professionals [153]. Neither questionnaire, however, replaces a thorough assessment by a multidisciplinary team with expertise in diabetes and eating disorders.

Treatment of eating disorders

There are no evidence-based treatments or comprehensive treatment protocols that lead to sustained improvements in glycaemia and diabetes-related outcomes in people with type 1 diabetes and eating disorders [148]. Consequently, advice is currently based on existing guidelines for people with diabetes or with eating disorders, with some pragmatic integration of the two [171, 172]. For example, the NICE guidance for the treatment of eating disorders now includes a subchapter with general principles for managing a person with diabetes [172]. Likewise, the NICE guidance for managing type 1 diabetes alerts the diabetes healthcare professionals to the possibility of bulimia nervosa, anorexia nervosa, and insulin dose manipulation in adults with type 1 diabetes with overconcern about body shape and weight, low BMI, hypoglycaemia, and suboptimal glucose management [171]. The key strategy is a multidisciplinary and multiprofessional team approach that integrates the physical and mental health aspects pertinent to both diabetes and eating disorders [150]. There are ongoing clinical research and clinical quality improvement projects in the UK that incorporate a multidisciplinary approach and step-wise re-insulinization, combined with psychotherapy and close monitoring of physical and mental health [173].

Although most people can be managed on an outpatient basis, the risk of impaired physical health necessitating inpatient admission is increased in those with diabetes. Regular physical monitoring is needed to manage the high risk of complications and mortality. Challenges in treating acute metabolic decompensation and inpatient care in eating disorder units for a person with T1DE lie in the combination of re-insulinization and refeeding that can cause dramatic shifts of electrolytes and fluids between extra- and intracellular compartments, sensation of pseudo-hypoglycaemia, rapid weight gain due to fluid retention, and stopping the catabolism by reintroducing insulin. Dehydration caused by hyperglycaemia mandates appropriate access to fluids, which is conflicting with standard eating disorder care where fluid overload to imitate weight gain is avoided by limitations of fluid intake. Nutrient and vitamin deficiency in combination with chronic hyperglycaemia and following rapid improvement of glycaemia can exacerbate autonomic and or painful peripheral neuropathy.

Severe T1DE has to be treated cautiously in a step-wise titration process to avoid treatment side effects, with a slow reduction of HbA_{1c} by no more than 20 mmol/mol (2%) in two months. Treatment-induced worsening of pre-existing retinopathy can occur following too rapid improvement of glycaemia, particularly in those with pre-existing diabetic retinopathy at baseline, and a large reduction in HbA_{1c} [174]. Retinal screening and assessment

are mandatory before initiating treatment that may result in rapid improvement of glycaemia. Another possible side effect of too rapid improvement is treatment-induced neuropathy, presenting as neuropathic pain, autonomic dysfunction, or a combination of both. As insulin neuritis can lead to severe, disabling pain, there should be a focus on controlling symptoms while they gradually improve over the subsequent weeks or months.

Psychotherapeutic treatment may include cognitive behavioural therapy, family therapy, or psychodynamic therapy among other approaches [175]. Ideally, there should be close collaboration between the psychotherapist and the diabetes team to avoid conflicting messages and to provide adequate training in the other specialism to enable joint care management using a stepwise approach that integrates both diabetes and eating disorder care. Dietary and refeeding plans should be coordinated with the diabetes therapy; some people with T1DE tend to prefer lower-carbohydrate diets (with ~150 g of carbohydrates/d) and so access to hypoglycaemia treatment carbohydrates and consideration of hypoglycaemia risk in those who purge are needed.

Insulin administration should be closely supervised, or even taken over by healthcare professionals in the inpatient setting, as insulin injections often are manipulated by those with a pervasive fear of insulin being weight gaining, in a similar way to supervised meal times in inpatient treatment of anorexia nervosa [173]. Insulin pump therapy is not indicated in the acute stages of severe T1DE due to risk of diabetic ketoacidosis, but may be reinstated in advanced stages of recovery on an individualized basis, if it is clinically safe.

Anorexia nervosa

A necessary first step for all is restoration of weight towards normal levels. During this process it is usually necessary to aim for slow stepwise glycaemia improvement rather than tight glycaemic management. Diet should focus on healthy foods with a high satiety index. Severe hypo- or hyperglycaemia must be avoided; as it is necessary to consume calories to prevent or treat hypoglycaemia, this can cause anxiety in the person with diabetes. Glucagon injections for treatment of severe hypoglycaemia are much less effective in people with anorexia nervosa and T1DE, as the glycogen stores are depleted. As the insulin dose and blood glucose levels will change with eating habits and weight, close liaison will be needed between the eating disorder and diabetes teams.

Bulimia nervosa

Treatment for bulimia nervosa, particularly by means of CBT, is widely accepted, although there has been less study of its suitability for people with diabetes. The coexistence of diabetes with bulimia inevitably complicates management. For example, purging by vomiting after a meal insulin bolus is associated with a high risk for hypoglycaemia. Successfully engaging people in treatment may be more difficult, and approaches such as motivational interviewing may play a role. Modification to standard treatment approaches includes the monitoring of self-care behaviours; again, it is desirable that the eating disorder team has knowledge and experience of the usual management of diabetes. Conflict may arise between the modifications to eating behaviour advocated for bulimia nervosa treatment (promoting a more flexible approach to eating) and the dietary advice often given for diabetes management (regular controlled eating and avoidance of certain food groups). The development of structured education that offers a more person-centred approach may help in this dilemma.

Other forms of treatment for bulimia nervosa include interpersonal psychotherapy and the use of antidepressants. Fluoxetine has been approved for acute and maintenance treatment of binge eating and vomiting behaviours in people with moderate to severe bulimia nervosa. A group educational programme for people with bulimia and type 1 diabetes was better than standard care in improving eating behaviour, but did not lead to improved glycaemic levels [176]. Inpatient treatment also appears to be successful, but relapse may occur rapidly after discharge [177]. The applicability of this approach in most healthcare systems remains to be tested.

Binge eating disorder

For the management of binge eating disorder, psychological treatments such as CBT are recommended as first line and supported by meta-analytic reviews [178]. Treatment approaches for binge eating disorder with comorbid diabetes have not been extensively studied, but in one small study in type 2 diabetes no significant difference was found in HbA_{1c} between those with and without binge eating disorder [179].

Psychotic disorders

Psychotic disorders include schizophrenia, psychotic depression, and bipolar disorder and are often known as *severe (and enduring) mental illness* (SMI). The presence of psychotic symptoms, which include delusions and hallucinations, has a profound effect on well-being and functioning of many aspects of daily life. When they co-occur with a chronic physical illness such as diabetes, they create complex management challenges.

Case definitions

Schizophrenia is characterized by psychotic symptoms (delusions, hallucinations), disorganization of speech and other behaviour, and so-called *negative* symptoms that include loss of drive and blunting of affect (Table 65.4). Schizophrenia is also associated with cognitive decline. The illness tends to run a chronic clinical course, and most people with the condition will be under the long-term care of specialist mental health services.

Although bipolar disorder is often thought to be a disease whose hallmark is the occurrence of one or more episodes of mania (elevated mood; Table 65.5), bipolar disorder can be conceptualized as predominantly a depressive disorder, based on the amount of time people with bipolar disorder have depressive symptoms [180]. On average, the ratio of the number of depressive episodes to manic or hypomanic episodes is 3 : 1 for bipolar I disorder, and the ratio of

Table 65.4 Diagnostic criteria for schizophrenia.

A. Two or more of the following symptoms, at least one of these must be (1), (2), or (3):
   1. Delusions.
   2. Hallucinations.
   3. Disorganized speech.
   4. Grossly disorganized or catatonic behavior.
   5. Negative symptoms (affective flattening, alogia, or avolition).

B. Social/occupational dysfunction.

C. Features continuously present for at least 6 months.

Source: American Psychiatric Association 2013 [14].

Table 65.5 Diagnostic criteria for a manic episode [14].

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week.
B. During the period of mood disturbance, three or more of the following symptoms have persisted (four if mood only irritable):
1. Inflated self-esteem or grandiosity.
2. Decreased need for sleep.
3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience that thoughts are racing.
5. Distractibility.
6. Increase in goal-directed activity or psychomotor agitation.
7. Excessive involvement in pleasurable activities that have high potential for painful consequences (e.g. spending, sexual activity).

C. Marked impairment in occupational functioning or in usual social activities or relationships with others, or need for hospitalization to prevent harm to self or others, or psychotic symptoms.

Source: American Psychiatric Association 2013 [14].

depressive episodes to hypomanic episodes is 39:1 for bipolar II disorder. In addition, the strict diagnostic criteria for bipolar disorders are complex, and there is a degree of overlap with schizophrenia, such that some people may be diagnosed as having a *schizo-affective* disorder [181].

Epidemiology

Schizophrenia is estimated to have a point prevalence of between 1 and 7 per 1000 in the general population, with an annual incidence of 13–70 per 100 000, and a lifetime risk of 1–2%. There is little variation in incidence across the world. The clinical course of the illness is variable, ranging from a single brief episode (rarely) to a lifelong illness with marked deterioration over time. There are many theories about the causation of schizophrenia; it has a marked genetic risk profile, but is also associated with early cerebral insults (e.g. birth anoxia) and environmental stress.

Bipolar disorder is much less common than unipolar depression, with an estimated lifetime prevalence of 1% for bipolar I disorder and another 1% for bipolar II disorder. Again, genetic factors are thought to play an important role in the aetiology of bipolar disorder, which is among the most heritable of mental disorders.

People with SMI have standardised mortality rates that are approximately two- to threefold higher than the general population, equating to a loss of 10–20 years of life [182]. The average life expectancy for men and women with schizophrenia in the UK is 62.8 years and 71.9 years, respectively [183]. While suicide and trauma account for the highest relative risk of death, the commonest causes of death are from physical illness, principally cardiovascular disease. Over the last 30 years, while the life expectancy of the general population has improved, this has not been experienced by people with SMI, leading to a widening health inequality gap [184, 185].

Diabetes and severe mental illness

It is challenging to obtain precise diabetes prevalence rates in people with SMI because of the high prevalence of undiagnosed diabetes, which is estimated to be up to 70% of all cases in some settings [3]. Nevertheless, there is a general consensus that the prevalence of diabetes is two- to threefold higher than in the general population. A meta-analysis of 118 studies including 438 245 individuals with SMI found that the estimated weighted mean prevalence of type 2 diabetes was 10.2% [186]. There were no significant differences in the estimated rates of diabetes between different SMIs, but diabetes was more common among women than men. Compared with the general population, people with multiple episodes of psychosis had significantly increased risk of type 2 diabetes (relative risk [RR] 1.85). The increased prevalence is driven by an excess of type 2 diabetes, as there is no evidence of enhanced pancreatic autoimmunity. The incidence of diabetes is higher and the onset of diabetes appears to be 10–20 years earlier than in the general population [187] (Figure 65.3). As is seen in the general population, Black and Asian minority background and socioeconomic deprivation increase risk of type 2 diabetes in people with SMI [188]. Furthermore, the incidence of diabetes increases with age until around the age of 60 years [188]; however, as diabetes is uncommon in young healthy adults, the increased relative risk of diabetes is greatest in adolescents and young adults with SMI [3].

Although subtle metabolic abnormalities have been found in people with a first episode of psychosis, the majority of studies show that metabolic abnormalities develop rapidly after treatment initiation and meta-analyses have found no appreciable increase in

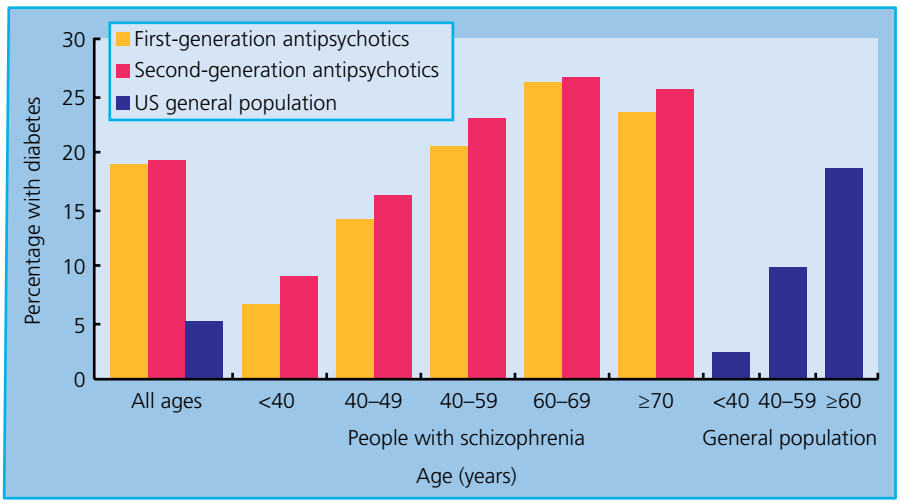


Figure 65.3 Age-specific prevalence rates of diabetes in people with schizophrenia compared with the general US population. Source: Data from Sernyak et al. 2002 [187] and National Health and Nutritional Examination Survey 2001–2002 (https://www.cdc.gov/nchs/nhanes/index.htm).

diabetes in people prior to the initiation of antipsychotic treatment [186, 189].

People with SMI experience higher rates of microvascular and macrovascular complications, acute metabolic dysregulation, and three- to fourfold more diabetes-related deaths [3]. In one study from Denmark, among those aged ≤50 years, 15.0% died within seven years of a diagnosis of diabetes; the corresponding figures for those aged 50–69 years and ≥70 years were 30.7% and 63.8%, respectively. A third of deaths from physical causes were attributed to diabetes, while 14% of deaths were attributed to the interaction between diabetes and SMI [190]. In a recent observational matched nested case–control study using routinely collected data from primary healthcare in England, SMI was associated with an almost twofold increased risk of all-cause mortality and more than twofold increased cardiovascular-specific mortality in people with diabetes [188].

Why psychotic disorders are linked to diabetes

Unlike depression, most evidence indicates that diabetes does not predispose to psychotic illness. Psychotic illnesses tend to present in early adulthood and precedes the onset of diabetes. While psychosis may also present in older age, it is unclear whether diabetes increases the risk of psychosis in this age group [191].

Conversely, it has been noted for over a century that people with SMI are at increased risk of glucose abnormalities [3]. An interest in the physical health of those with SMI was stimulated following the introduction of first-generation antipsychotics that for the first time allowed people with SMI to achieve reasonable control of their psychotic symptoms and live independently. Following concerns about metabolic side effects of the second-generation antipsychotics around the turn of the millennium, further effort was made to understand the link between psychosis and diabetes, and a greater comprehension of the highly complex inter-relationship between the person with SMI, their treatment and environment, and risk of diabetes has been gained. Although concerns about the side effects of antipsychotics triggered the resurgent interest in diabetes, to blame the antipsychotics alone for the increased risk of diabetes misses the full picture and may hinder attempts to prevent and treat diabetes in this population.

Genetics

Both schizophrenia and type 2 diabetes are highly heritable disorders and it is conceivable that there may be genes that increase the risk of both conditions. Many schizophrenia genes are expressed in the brain and include those involved in glutamatergic neurotransmission and the D_2 dopamine receptor (*DRD2* gene), while type 2 diabetes is associated with polymorphisms in genes that influence hepatic and peripheral insulin resistance, adipogenesis, and pancreatic β-cell mass and function (Chapter 12). Recent studies have identified at least 37 common genes that increase the risk of both type 2 diabetes and schizophrenia [192]. It is estimated that ~11% and 14% of these risk genes for type 2 diabetes and schizophrenia, respectively, may account for the risk of the other disease. Several candidate genes that may affect the risk of both conditions have been identified (Table 65.6) [192, 193].

In addition to affecting an individual's risk of type 2 diabetes directly, genetic polymorphisms in various genes, including the promoter region of the 5-hydroxytryptamine$_{2C}$ receptor, leptin, methylenetetrahydrofolate reductase (*MTHFR*), and *MC4R* genes, appear to modify the risk of antipsychotic-induced weight gain [194]. Polymorphisms in the *HRH1*, *BDNF*, *NPY*, *CNR1*, *GHRL*, *FTO*, and *AMPK* genes may also affect the risk of weight gain.

Table 65.6 Genes that have been linked to both diabetes and schizophrenia.

Gene	Function
Glycogen synthase kinase 3 (*GSK3*)	Regulates both glucose metabolism and cognitive function
Serine–threonine protein kinase *AKT1*	Reduced expression in lymphocytes and the frontal cortex in schizophrenia. Mediates insulin signalling and glucose metabolism; reduced action leads to diminished phosphorylation of its substrates, including *GSK3*
Dopamine D_2 receptor (*DRD2*) gene	Implicated in obesity and type 2 diabetes, through alteration of insulin sensitivity and secretion. Affects risk of schizophrenia
Tyrosine hydroxylase gene	Associated with insulin resistance and schizophrenia
TCF7L2 gene	Encodes for a transcription factor involved in Wnt/beta-catenin signalling that has a role in pancreatic β-cell function and is a susceptibility gene for type 2 diabetes. Wnt signalling pathway plays a role in central nervous system development and is associated with schizophrenia
Brain-derived neurotrophic factor and related pathway genes	Major member of the neurotrophin family, which has been linked with a range of clinical features of schizophrenia and is involved in regulation of cardiometabolic function

Source: Data from Lin and Shuldiner 2010 [192] and Perry et al. 2022 [193].

Environment and biological effects of the illness

Many of the environmental factors that mediate the association between diabetes and depression are also relevant for the links between diabetes and SMI, including intra-uterine environment, adult health behaviours (diet and physical activity), neighbourhood environment, and poverty (Figure 65.2) [3]. Several inflammatory and neuroendocrine changes, including HPA dysfunction, also occur in SMI.

Antipsychotic medication

Antipsychotics are an integral element of the treatment of SMI that also comprises multidisciplinary psychological, social, and rehabilitation interventions. They are frequently taken over a long period to prevent relapse and hospitalization and to decrease mortality [195]. The first generation of antipsychotics was introduced in the 1950s, but their use was blighted by a high incidence of a range of unwanted side effects, including hypotension, weight gain, sexual dysfunction, sedation and extrapyramidal side effects. In order to reduce the likelihood of these movement disorders, second-generation antipsychotics (also known as atypical antipsychotics) were developed. Although the second-generation antipsychotics are generally better tolerated, an association with weight gain and other metabolic abnormalities rapidly became apparent [196].

Large pharmaco-epidemiological database studies reported that antipsychotics were associated with more diabetes than no treatment, while treatment with a second-generation antipsychotic is associated with a 32% (15–51%) increase in diabetes risk compared with first-generation antipsychotics (Figure 65.4) [197]. Overall, the risk appears to be low, however, with number needed to harm (NNH) estimates ranging from 19 to 333 for clozapine, 22 to 3333 for risperidone, 21 to 747 for olanzapine, and 24 to 500 for quetiapine [198]. Although the risk of diabetes for the latest

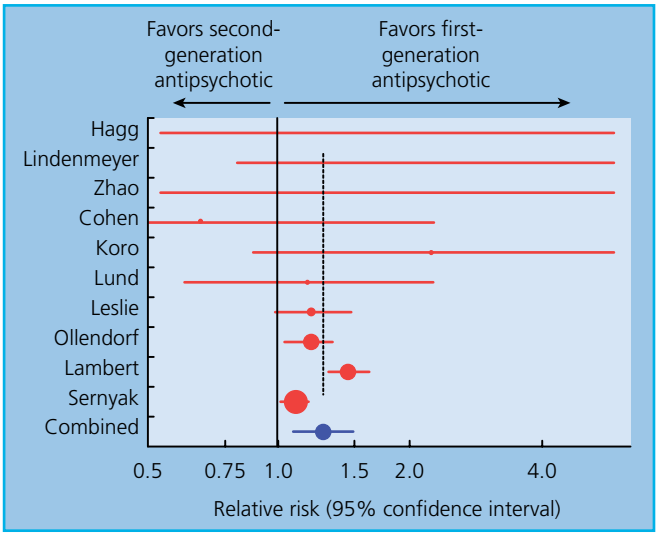


Figure 65.4 Forest plot of relative risks and 95% confidence intervals for diabetes in individuals with schizophrenia receiving first-generation antipsychotics compared with second-generation antipsychotics. Source: Modified from Smith et al. 2008 [197].

second-generation antipsychotics is widely believed to be lower, this has not always been apparent in pharmaco-epidemiology studies. For example, aripiprazole and ziprasidone were not associated with lower rates of diabetes than olanzapine, quetiapine, and risperidone in a pharmaceutical claims database [199], perhaps because of channelling bias, whereby people at higher risk for diabetes are prescribed antipsychotics that are perceived to be safer.

Although pharmaco-epidemiological studies can assess small risks in large populations who may be followed for a longer period of time than clinical trials by design, methodological flaws can affect the interpretation of results. They rely on data from administrative databases with inherent problems of data quality, such as convenience reporting of adverse effects, prescriber bias, and omission of important confounding diabetes risk factors [200]. Furthermore, individuals with either undiagnosed diabetes or those treated with lifestyle interventions alone will not be recorded in prescription databases.

Treatment assignment is not randomized and so differences in diabetes rates may be explained by factors other than the treatment. For example, clozapine is usually reserved as a second-line antipsychotic because of its risk of causing agranulocytosis, requiring ongoing monitoring of the white blood cell count. As a result, it is used in people with the most serious mental illness who are resistant to treatment with at least two other antipsychotics. By virtue of their illness, these individuals may be at higher risk of diabetes, and so higher rates of diabetes among people treated with clozapine may reflect a person receiving the antipsychotic rather than treatment *per se*. Another potential reason for the observed increase with clozapine is *screening bias*. People receiving second-generation antipsychotics, particular those receiving clozapine, are much more likely to be screened for blood glucose abnormalities than individuals receiving first-generation antipsychotics [201]. Since there are high rates of undiagnosed diabetes in people with SMI, increased screening will inevitably result in an increased detection of diabetes without the need to invoke a causal relationship between drug and diabetes.

RCTs are considered the gold standard when assessing the effect of an intervention, but antipsychotic trials are underpowered to detect changes in incident diabetes and consequently most trials have reported no differences [202]. Examining blood glucose changes is a more sensitive way of assessing an antipsychotic's metabolic effects, and a systematic review of 48 head-to-head comparison studies found a greater, albeit small, increase in glucose following treatment with olanzapine compared with amisulpride, aripiprazole, quetiapine, risperidone, and ziprasidone [203]. There were no differences in glucose changes between the other antipsychotics studied. Another systematic review found similar increases in glucose following treatment with the newer antipsychotics asenapine, iloperidone, and paliperidone [204]. In the European First-Episode Schizophrenia Trial, which examined treatment effects in treatment-naïve people with first-episode psychosis, the mean change in glucose over a year ranged between 0.2 and 0.5 mmol/l, with no differences between drugs [205]. Although small, these increases in glucose concentration may translate into meaningful differences in incident diabetes with the long duration of treatment needed to treat SMI.

There are several mechanisms by which antipsychotics increase the risk of diabetes. All antipsychotics may be associated with weight gain [196]; however, the effect size is markedly heterogeneous, with weight gain being less problematic for haloperidol, ziprasidone, and lurasidone in contrast to large effects observed with olanzapine, zotepine, and clozapine (Table 65.7) [206]. Overall, 15–72% of treated individuals experience more than 7% of body weight gain in the first year of treatment [207]. From the short-term pivotal trials of the different antipsychotics, the NNH versus placebo for weight gain of ≥7% from baseline ranges from 6 for olanzapine and quetiapine immediate release to 67 for lurasidone [208]. Weight gain is most marked in people naïve to antipsychotics, where weight gain is up to three- to fourfold greater than in those with chronic illness [209]. Most weight gain occurs early in treatment, although people can continue to gain weight for at least four years after treatment initiation, albeit at a slower rate and gradually reaching a plateau.

Weight does not explain all the excess diabetes risk, as some individuals develop diabetes without being overweight or gaining weight. As weight gain is likely to increase diabetes risk through

Table 65.7 Hierarchy of risk of weight gain with various antipsychotic medications. The highest risk is listed at the top.

- Olanzapine
- Zotepine
- Clozapine
- Iloperidone
- Chlorpromazine
- Sertindole
- Quetiapine
- Risperidone
- Paliperidone
- Asenapine
- Aripiprazole
- Lurasidone[a]
- Ziprasidone[a]
- Haloperidol[a]

[a] No significant difference from placebo.
Source: Data from Leucht et al. 2013 [206].

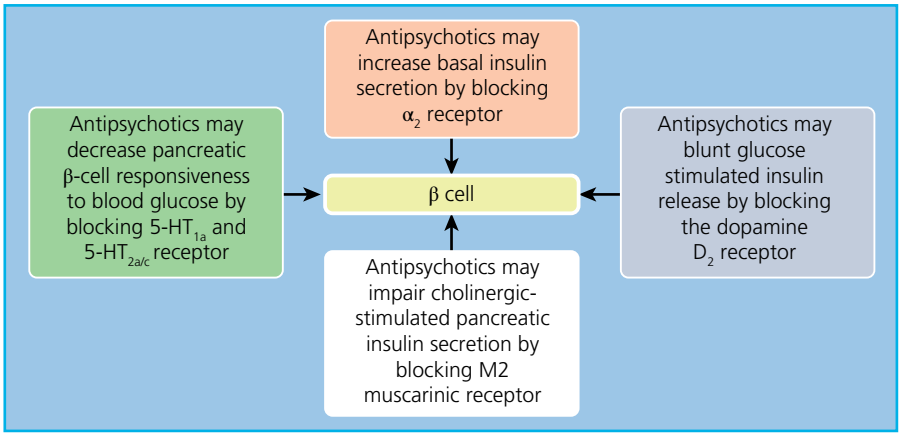


Figure 65.5 Possible pharmacological effects of antipsychotics on β-cell function.

increased insulin resistance, it does not explain why some people develop diabetic ketoacidosis, which occurs as a result of markedly impaired insulin secretion. Through their interaction with multiple receptors, antipsychotics may affect insulin secretion by the β cells of the pancreas. Blockade of α_2 receptors may increase basal insulin secretion, while blockade of 5-HT_{1a} and 5-$HT_{2a/c}$ receptors may decrease pancreatic β-cell responsiveness to blood glucose (Figure 65.5). Central control of glucose homeostasis may also be affected by antipsychotics [210]. In addition to these pancreatic effects, *in vitro* work suggests that antipsychotics may directly impair insulin action by inhibiting insulin-mediated glucose uptake and glycogen synthesis.

Contribution of different mechanisms

Given the complex pathophysiology of type 2 diabetes, it is perhaps unsurprising that multiple mechanisms are involved in the association between SMI and diabetes. It is also likely that the contributions of these risk factors operate differently between individuals. Overall, it appears that an excess of traditional diabetes risk factors, such as obesity, poor diet, physical inactivity, and family history, conveys a higher risk than treatment, but this does not discount the possibility that antipsychotics are the major contributor to the development of diabetes in certain individuals, particularly where the onset of diabetes is rapid after treatment initiation and other risk factors are absent [3].

Screening of diabetes in those with severe mental illness

Given the large numbers with undiagnosed diabetes, there have been moves to screen at-risk individuals in the general population for diabetes. As people with SMI constitute a high-risk group, several national and international guidelines have recommended regular screening for diabetes, regardless of antipsychotic treatment (Table 65.8) [212, 213]. Although there are differences in detail, all guidelines recommend screening before the start or change of treatment, several months later to identify the few who develop diabetes rapidly after antipsychotic initiation, and annually thereafter. Although the oral glucose tolerance test has been implemented successfully in some settings, this test is no longer widely used in the general population and measurements of fasting or random glucose, or HbA_{1c}, are more practical alternatives. There is a debate about the relative sensitivity and specificity of each of these tests, but a pragmatic view should be taken; both random glucose and HbA_{1c} are more convenient and this probably outweighs any small loss of sensitivity. One caveat about HbA_{1c} is that it may be falsely negative if glucose concentrations are rising rapidly, as may happen shortly after treatment initiation. In the setting, combining HbA_{1c} and glucose is a sensible option.

Table 65.8 Recommended screening for cardiovascular disease risk.

	Baseline	3 monthly	Annually
Medical history	✓	✓	✓
Height	✓		
Weight	✓	Every visit during first 6–8 weeks of treatment. At least quarterly thereafter	✓
Blood pressure	✓	✓	✓
Glucose[a]	✓	✓	✓
HbA_{1c}	✓	(✓)	✓
Lipid profile	✓	✓	✓
ECG	✓	✓	✓

[a] Either fasting or random. Oral glucose tolerance test only rarely indicated. Be aware HbA_{1c} may be normal if glucose is changing rapidly.
ECG, electrocardiogram; HbA_{1c}, glycated haemoglobin.
Source: Data from Holt 2015 [211].

Despite clear guidance and potential benefit, screening has not been implemented into routine clinical practice (Figure 65.6) [214, 215], perhaps because people with SMI may be less likely to undergo opportunistic health screening. Professional barriers to screening, including inertia or prejudice, lack of clarity about whose responsibility it is, lack of understanding about the most appropriate test and its interpretation, and lack of access to necessary equipment, may also be responsible for the poor screening rates within mental health settings [216]. In the UK, general practitioners are offered financial incentives through the Quality Outcomes Framework to improve routine physical health checks for people with SMI, including screening for and monitoring of diabetes.

Prevention of diabetes

There have been no specific diabetes-prevention studies in people with SMI, but RCTs of lifestyle interventions that aim to treat or prevent obesity, which encompass similar principles to diabetes prevention, have been undertaken. Despite widespread pessimism that lifestyle interventions in people with SMI would be ineffective, the early studies suggested the contrary [217]. A meta-analysis of lifestyle interventions reported a mean reduction in weight of

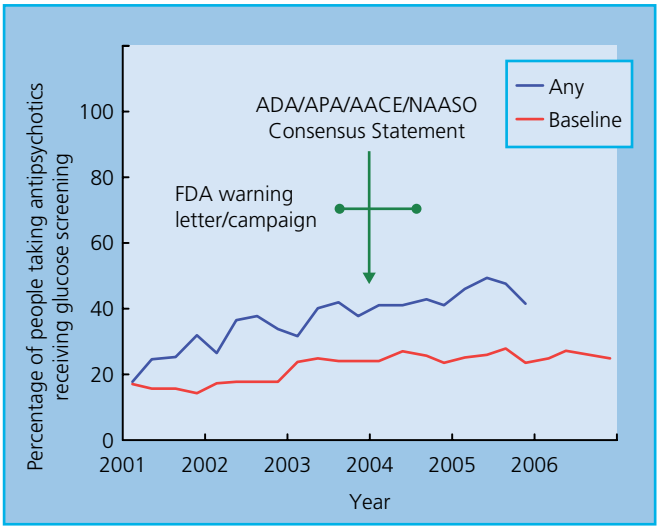


Figure 65.6 The effect of the American Diabetes Association (ADA), American Psychiatric Association (APA), American Association of Clinical Endocrinologists (AACE), and North American Association for the Study of Obesity (NAASO) consensus statement and US Food and Drug Administration (FDA) guidance on glucose testing in people receiving antipsychotic medication. Source: Modified from Morrato et al. 2009 [214], Figures 1 and 2.

Table 65.9 Drugs that have been tested as potential agents to prevent or reduce weight gain.

Amantadine
Nizatidine
Topiramate
Metformin
Betahistine
Fluoxetine
Reboxetine (not available in the USA)
Sibutramine (withdrawn because of safety concerns)
Exenatide
Orlistat (approved for the management of obesity)
Lorcaserin (withdrawn because of safety concerns)
Phentermine topiramate combination (approved for the management of obesity in the USA)
Naltrexone bupropion combination (approved for the management of obesity in the USA)
Liraglutide (approved for the management of obesity)

3.12 kg over a period of 8–24 weeks, with commensurate reductions in waist circumference and improvements in cardiovascular risk factors [217]. The conclusions were, however, limited by the short duration of most trials (12–16 weeks) and the low number of participants (median 53, range 15–110). NICE published an expanded literature review of 24 studies in 2014 that came to broadly the same conclusions but was more critical of the evidence, highlighting the high risk of bias and substantial heterogeneity of effect size between studies [213]. The most recent meta-analysis, which included 41 RCTs and 4267 participants, reported a much smaller effect size that is likely not to be clinically relevant [218]. Overall the interventions reduced mean BMI by 0.63 kg/m^2, equivalent to a weight loss of 2.2 kg, in association with a reduction of waist circumference. Intervention participants were 50% more likely to lose weight than control participants. More recent and more rigorous studies were less likely to demonstrate a beneficial effect [219, 220], which may explain the smaller effect size than in earlier meta-analyses.

No pharmacological diabetes-prevention trials in people with schizophrenia have been reported, but short-term trials of various drugs have been undertaken to reduce weight or attenuate weight gain in people with schizophrenia receiving antipsychotics. Although metformin has very little effect on body weight in the general population, this drug is the most extensively studied in the context of SMI and is associated with a mean reduction in body weight of 3.3 kg over 3–6 months [221]; it is unclear, however, whether this weight loss is maintained in the long term. Many other drugs have been studied, of which orlistat, reboxetine, and topiramate are associated with a small reduction in weight; however, no drugs have been sufficiently evaluated to recommend their routine use, not least because of their potential for adverse effects (Table 65.9) [222].

The most promising new drug class is the glucagon-like peptide-1 (GLP-1) receptor agonists. Three studies have evaluated the use of GLP-1 receptor agonists using the diabetes dose as a treatment for antipsychotic-induced weight gain, two using exenatide and one using liraglutide [223–225]. A meta-analysis of these studies reported a mean 3.71 kg greater weight loss after 16 weeks of treatment in people treated with the GLP-1 receptor agonists [226]. Weight loss was greater in those treated with clozapine or olanzapine compared with other antipsychotics. A further trial of the 3 mg obesity dose of liraglutide demonstrated a 5.7 kg weight loss in people with schizophrenia [227].

Given the varying propensities to weight gain and metabolic disturbance associated with different antipsychotics, it is reasonable to consider whether switching antipsychotics may reduce the subsequent risk of diabetes. A meta-analysis of 40 RCTs and 15 uncontrolled studies including 12 279 individuals found reducing that the dose, discontinuing the antipsychotic, or switching to a partial agonist antipsychotic reduced weight by a mean of 1.5 kg compared to maintaining the current treatment. This suggests that altering the antipsychotic will reverse only part of antipsychotic-induced weight gain [228].

Management of those with diabetes

The management of diabetes in people with SMI should follow currently available treatment algorithms for the general population, but agents that induce less weight gain or promote weight loss, such as incretin-based therapies or sodium–glucose cotransporter 2 (SGLT-2) inhibitors, may have advantages given the high prevalence of obesity in people with SMI.

Diabetes self-management is key to managing diabetes and there are concerns that SMI may interfere with the lifestyle changes, regular monitoring, and self-medicating that make up diabetes self-management. Consequently, it is reassuring that a systematic review reported medication-taking rates among those with mental illness of between 51% and 85%, with two studies finding higher rates than in the general population [229]. Nevertheless, living with and managing both diabetes and SMI imposes a considerable burden, which often results in diabetes being overshadowed by the more immediate challenges arising from the mental illness [230]. Tailored diabetes education and self-management support for people with SMI is needed, and evaluation of the effectiveness of such approaches is an identified research gap [230, 231].

When an individual develops diabetes while receiving an antipsychotic, it is important to assess what role this is likely to have played in the onset of diabetes. Under some circumstances, it may be appropriate to switch to an alternative antipsychotic if the mental state will not be adversely affected [212].

It is important that healthcare professionals, both in primary care and in mental health teams, ensure that people with SMI are not disadvantaged with regard to their diabetes care. Despite increased contact with primary care, there is evidence that people with mental illness receive less education about diabetes, are less likely to be examined for retinopathy or diabetic foot complications, and are less likely to be screened for HbA_{1c} and other cardiovascular risk factors [6].

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66 Social Aspects of Diabetes

Brian M. Frier[1] and Mark W.J. Strachan[2]

[1] Centre for Cardiovascular Science, The Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK

[2] Metabolic Unit, Western General Hospital, Edinburgh, UK

Key points

Driving

- Potential hazards facing the driver with diabetes include hypoglycaemia, visual impairment, and disability from severe neuropathy or leg amputation.
- Hypoglycaemia can severely disrupt driving skills by causing cognitive dysfunction and mood changes. Motor skills and judgement may become impaired when blood glucose falls before hypoglycaemic symptoms are experienced. Impaired awareness of hypoglycaemia is a relative contraindication to driving. Drivers with diabetes must take precautions to avoid hypoglycaemia and know how to treat it if it occurs while driving.
- Corrected visual acuity that is worse than 6/12 in the better eye precludes driving in the general population. People with diabetes may fulfil this criterion, but still have significant visual impairment (e.g. field loss, poor night vision, and perception of movement) secondary to retinopathy, laser treatment, or cataracts.
- In many countries, drivers with diabetes are legally required to declare the diagnosis for their driving licence and motor insurance. Failure to do this will invalidate insurance claims.
- Driving licences are often issued for fixed terms and only renewed following satisfactory medical review. In many countries, insulin-treated drivers are debarred from driving passenger-carrying vehicles and large goods vehicles, although the regulations in Europe have been changed to allow this. In other parts of the world no such licensing restrictions exist, to the detriment of safe driving and public safety.

Employment

- Diabetes is not a bar to most occupations, and people with diabetes are protected in many countries by legislation against discrimination on the grounds of disability.
- People with insulin-treated diabetes are barred from certain occupations because of the risk of hypoglycaemia. These include the armed forces, emergency services, commercial pilots (in some countries), prison and security services, and jobs in potentially dangerous areas (e.g. at heights, underwater, and offshore).
- Severe hypoglycaemia in the workplace is uncommon and shift work seldom compromises glycaemic management. Depressive illness and diabetes-related disability are associated with higher unemployment and sickness absence in people with diabetes.

Prison and Custody

- Glycaemic levels may be suboptimal in prison because of restrictions in diet, exercise, and blood glucose monitoring. Intercurrent illness and metabolic abnormalities may not be recognized or treated promptly.
- Input from a diabetes specialist may improve the quality of care. Knowledge of diabetes among prison officers and staff of short-term custodial units is often limited and may be improved by liaising with local diabetes specialist services.

Insurance

- Diabetes should be declared to insurers, who may impose higher premiums or limited coverage. Many insurers' decisions are based on outdated actuarial data or misconceptions about the current prognosis of diabetes. National diabetes organizations can provide details of insurance brokers who do not weight policies against people with diabetes.
- Life expectancy in type 1 diabetes can be modelled from age, sex, and the presence of proliferative retinopathy and nephropathy. As the latter is a major determinant of survival, life insurance premiums should be reduced for all those who reach the age of 50 years with no evidence of renal impairment.

Alcohol

- The association between excessive alcohol consumption, chronic pancreatitis, and secondary diabetes is well established. Alcohol excess is also associated with central obesity and poor medication taking; both could increase the risk of type 2 diabetes and compromise the management of established diabetes. Most epidemiological studies, however, have demonstrated a J-shaped relationship between alcohol consumption and diabetes, with moderate intake being associated with a lower risk of diabetes.
- In type 2 diabetes, moderate alcohol consumption is associated with a 35% reduction in total mortality and lower risk of cardiovascular disease compared to abstinence. Excessive alcohol consumption is associated with hypertriglyceridaemia and resistant hypertension; affected individuals have an increased vascular risk.
- Ethanol inhibits hepatic gluconeogenesis and increases the risk, severity, and duration of hypoglycaemia. Alcohol obscures the ability, both of the individual and of observers, to recognize and treat hypoglycaemia, and intoxication can simulate hypoglycaemia.

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Recreational Drugs

- Approximately one-third of young people with diabetes use recreational drugs at some time. The most common class of drug taken is cannabis, but nitrous oxide, amfetamine-type stimulants (including ecstasy), cocaine, and opiates are also used. New psychoactive drugs are also increasingly popular.
- Recreational drug use is associated with a sixfold higher risk of death from acute metabolic complications of diabetes. Intravenous drug use is uncommon, but is dangerous and is associated with omission of insulin therapy, frequent hospital admissions (usually with diabetic ketoacidosis), and high mortality.
- Cocaine and amfetamine-type stimulants can have profound haemodynamic effects through sympatho-adrenal activation. In addition to an increased risk of cardiac arrhythmias and myocardial ischaemia, the sympathetic activation antagonizes the action of insulin and can precipitate diabetic ketoacidosis.

Travel

- Diabetes is not a bar to travelling, but changes in meals, physical activity, and anti-diabetes drug treatment on route and after arrival all need careful consideration. Important issues include travel insurance, medical identification, supplies and storage of medication and monitoring equipment, and immunizations.
- During long flights, blood glucose should be monitored frequently and glycaemic levels relaxed to avoid hypoglycaemia. Insulin injection schedules may require in-flight adjustment, especially if the time shift exceeds four hours.

Leaving Home

- In the Diabetes UK Cohort Study, living alone was associated with a more than fourfold increase in risk of death from acute metabolic complications of diabetes.
- Leaving home is potentially a period of high risk for young people with diabetes; particular concern has been expressed about the welfare of university students with type 1 diabetes.

Diabetes influences many aspects of daily life, principally through the effects of treatment and its potential side effects, particularly hypoglycaemia. The development of diabetes-related complications, such as neuropathy and retinopathy, can also affect everyday activities, particularly when these are severe with clinical manifestations, or require time-consuming treatment such as dialysis for chronic renal failure.

Driving

Driving is an everyday activity that demands complex psychomotor skills, visuospatial coordination, vigilance, and satisfactory judgement. Although road traffic accidents are common, medical disabilities are seldom responsible. Diabetes is designated a *prospective disability* for driving because of its potential to progress and cause complications, while side effects of treatment (principally hypoglycaemia) can affect driving performance. In most high-income countries, the duration of the licence of a driver with diabetes is period restricted by law, and its renewal is subject to review of medical fitness to drive. The problems associated with diabetes and driving, and the limitations of relevant research data, have been reviewed [1, 2].

The main problems for the driver with diabetes are hypoglycaemia and visual impairment resulting from cataract or retinopathy. Rarely, peripheral neuropathy, peripheral vascular disease, and lower-limb amputation can present mechanical difficulties with driving (Table 66.1), but these problems may be overcome by adapting the vehicle and using automatic transmission systems.

Despite these challenges, drivers with diabetes do not appear to be involved in more accidents than their counterparts without diabetes [3]. Population studies have shown no excess in accident rates among drivers with diabetes in Northern Ireland [4], Scotland [5], England [6], Germany [7], Iceland [8], or Pittsburgh in the USA [9], while a large survey of over 30 000 drivers in Wisconsin, USA, found only a modest increase [10]. In most surveys, however, incidents were self-reported and probably underestimated, while fatal accidents (in which a diabetes-related cause, such as hypoglycaemia, could have had a role) were excluded. Accident rates may also have been lowered by regulatory authorities debarring high-risk drivers and by drivers with advancing diabetes-related complications who stop driving voluntarily [4, 5]. Practical advice for drivers with diabetes is given in Table 66.2.

Table 66.1 Reasons for drivers with diabetes to cease driving.

Newly diagnosed people with diabetes, especially insulin-treated, should not drive until glycaemic levels and vision are stable
Recurrent daytime hypoglycaemia (particularly if severe)
Impaired awareness of hypoglycaemia, if disabling
Reduced visual acuity in both eyes (worse than 6/12 on Snellen chart) – note that use of mydriatics for eye examination will affect visual acuity
Severe sensorimotor peripheral neuropathy, especially with loss of proprioception
Severe peripheral vascular disease
Lower-limb amputation

Table 66.2 Advice for drivers with diabetes.

Inform licensing authority[a] (statutory requirement) and motor insurer of diabetes and its treatment
Do not drive if eyesight deteriorates suddenly
Check blood glucose before driving (even on short journeys) and at intervals on longer journeys
Flash glucose monitoring and real-time continuous glucose monitoring (CGM) can also be used
Take frequent rests with snacks or meals; avoid drinking alcohol
Keep a supply of fast-acting and complex carbohydrate in the vehicle for emergency use
Carry personal identification to indicate the driver has diabetes (and is prone to hypoglycaemia)
If hypoglycaemia develops, stop driving, switch off engine, leave the driver's seat, and then treat with carbohydrate
Do not resume driving for 45 min after blood glucose has returned to normal (delayed cognitive recovery)

[a] In the UK, the licensing authority is the Driver and Vehicle Licensing Agency (DVLA), Swansea, SA99 1TU, UK.

Hypoglycaemia

Drivers with insulin-treated diabetes often experience hypoglycaemia while driving [4, 5, 11] and this can interfere with driving skills by causing cognitive dysfunction, even during relatively mild hypoglycaemia that does not induce symptoms. Studies of people with type 1 diabetes using a driving simulator showed that driving performance often became impaired at arterialized blood glucose concentrations of 3.4–3.8 mmol/l and deteriorated further at lower levels [12]. Problems included poor road positioning, driving too fast or too slow, inappropriate braking, and causing crashes by stopping suddenly. Alarmingly, most did not experience hypoglycaemic symptoms or doubt their competence to drive; only one-third treated the hypoglycaemia, and only when blood glucose had fallen below 2.8 mmol/l [12]. In the UK, the Driver and Vehicle Licensing Agency (DVLA) does not distinguish between type of diabetes, and the restrictions are based on the use of insulin as therapy, as this can cause hypoglycaemia in any person using this treatment. The risk of hypoglycaemia in insulin-treated type 2 diabetes rises with duration of insulin therapy.

Judgement and insight become impaired during hypoglycaemia, and some drivers with diabetes describe episodes of irrational and compulsive behaviour while at the wheel [11, 12]. Hypoglycaemia also causes potentially dangerous mood changes, including irritability and anger [13]. In addition, asymptomatic hypoglycaemia impairs visual information processing and contrast sensitivity, particularly in poor visibility [14, 15], which may diminish driving performance.

Poor perception of hypoglycaemia is also potentially dangerous. Many drivers with diabetes subjectively overestimate their current blood glucose level and feel competent to drive when they are actually hypoglycaemic [16]. Impaired awareness of hypoglycaemia, often associated with more frequent severe episodes, is potentially hazardous and is a common reason for revocation of the driving licence. It is not an absolute contraindication to driving if it can be demonstrated, by frequent self-monitoring, that there is prolonged freedom from hypoglycaemia [17].

Hypoglycaemia is a recognized cause of motor vehicle incidents, but its true frequency and causal relationship to a particular incident are often difficult to ascertain. Blood glucose is seldom estimated immediately after a road traffic accident, and evidence for preceding hypoglycaemia is typically circumstantial. Hypoglycaemia was the main cause of non-fatal motor vehicle accidents in the Diabetes Control and Complications Trial; hypoglycaemia was three times more common in the intensively treated participants, but the rate of major accidents was no higher, perhaps because of better precautionary advice [18]. Other studies have found that the frequency of hypoglycaemic episodes during driving correlates with the total number of accidents [4, 5] and hypoglycaemia-related driving mishaps are related to the frequency of severe hypoglycaemia in the preceding year [19]. The frequency of hypoglycaemia-related accidents is substantially lower than those caused by alcohol and drugs.

Avoiding and treating hypoglycaemia while driving

General measures to avoid hypoglycaemia are discussed in Chapter 40. All drivers with insulin-treated diabetes should keep some fast-acting carbohydrate in the vehicle; disturbingly, some do not [20]. Each car journey, no matter how short, should be planned in advance to anticipate possible risks for hypoglycaemia, such as traffic delays. It is essential to check glucose before and every two hours during long journeys, and to take frequent rests and meals. Unfortunately, these measures are not always undertaken [20, 21]. The use of intermittently scanned (flash) and real-time continuous glucose monitoring (CGM), where the device has an alarm, may alert the driver to a falling glucose concentration [22]. Driving expends energy and – as with other forms of exercise – prophylactic carbohydrate should be taken if the blood glucose is <5.0 mmol/l and driving should be avoided if <4.0 mmol/l [23].

If hypoglycaemia occurs during driving, the car should be stopped in a safe place, and the engine switched off before the driver consumes some glucose. In the UK, the individual should vacate the driver's seat and remove the keys from the ignition, as a charge can be brought for driving while under the influence of a drug (insulin) even if the car is stationary. Driving should not be resumed for at least 45 minutes after blood glucose has returned to normal, because cognitive function is slow to recover after hypoglycaemia [13].

Many features of hypoglycaemia resemble alcohol intoxication, and mentally obtunded hypoglycaemic drivers with diabetes are sometimes arrested on the mistaken assumption that they are inebriated. Drivers with insulin-treated diabetes should therefore carry a card or identity bracelet stating the diagnosis. Individuals with newly diagnosed insulin-treated diabetes may have to stop driving temporarily until their glycaemic levels are stable.

Insulin secretagogues, sulfonylureas and glinides, are the only oral anti-diabetes drugs that may cause hypoglycaemia while driving, and people treated with these agents should be informed of this possibility. While glucagon-like peptide 1 (GLP-1) receptor agonists alone are not associated with a risk of hypoglycaemia, this may be a problem when they are used in combination with a sulfonylurea. Blood glucose testing in relation to driving is not a requisite for drivers with Group 1 driving licences (see later), but may be required for holders of Group 2 driving licences who are taking this treatment combination.

Visual impairment

In the UK, monocular vision is accepted for driving, provided that the person meets the minimum legal requirement; that is, to be able to read a number plate with letters 8.9 cm high at a distance of 30 m, wearing spectacles if necessary. This corresponds to a distance visual acuity of approximately 6/10 on the Snellen chart. The number plate test has deficiencies: it is poorly reproducible under clinical conditions and does not assess visual fields, night vision, or the ability to see moving objects. All of these may be severely reduced by retinal ischaemia in pre-proliferative retinopathy [24], while visual field loss can be caused by extensive laser photocoagulation for diabetic retinopathy [25, 26] or macular oedema (Figure 66.1) [27]; careful containment of laser burns can preserve vision [28]. Cataracts often accentuate glare from headlights, and in such cases driving in the dark should be avoided.

Previous surveys have identified very few drivers with diabetes who would fail the standard eyesight test. Impaired vision is an uncommon reason for the driving licence to be refused or revoked, although many people stop driving voluntarily because their eyesight is deteriorating. Worsening vision from diabetic (or other) eye disease should be reported by the individual to the licensing authority.

Eye screening is a crucial part of assessing medical fitness to drive. Pupillary dilatation for fundoscopy or retinal photography temporarily reduces visual acuity, particularly if the usual binocular visual acuity is 6/9 or worse [29]. People with diabetes should

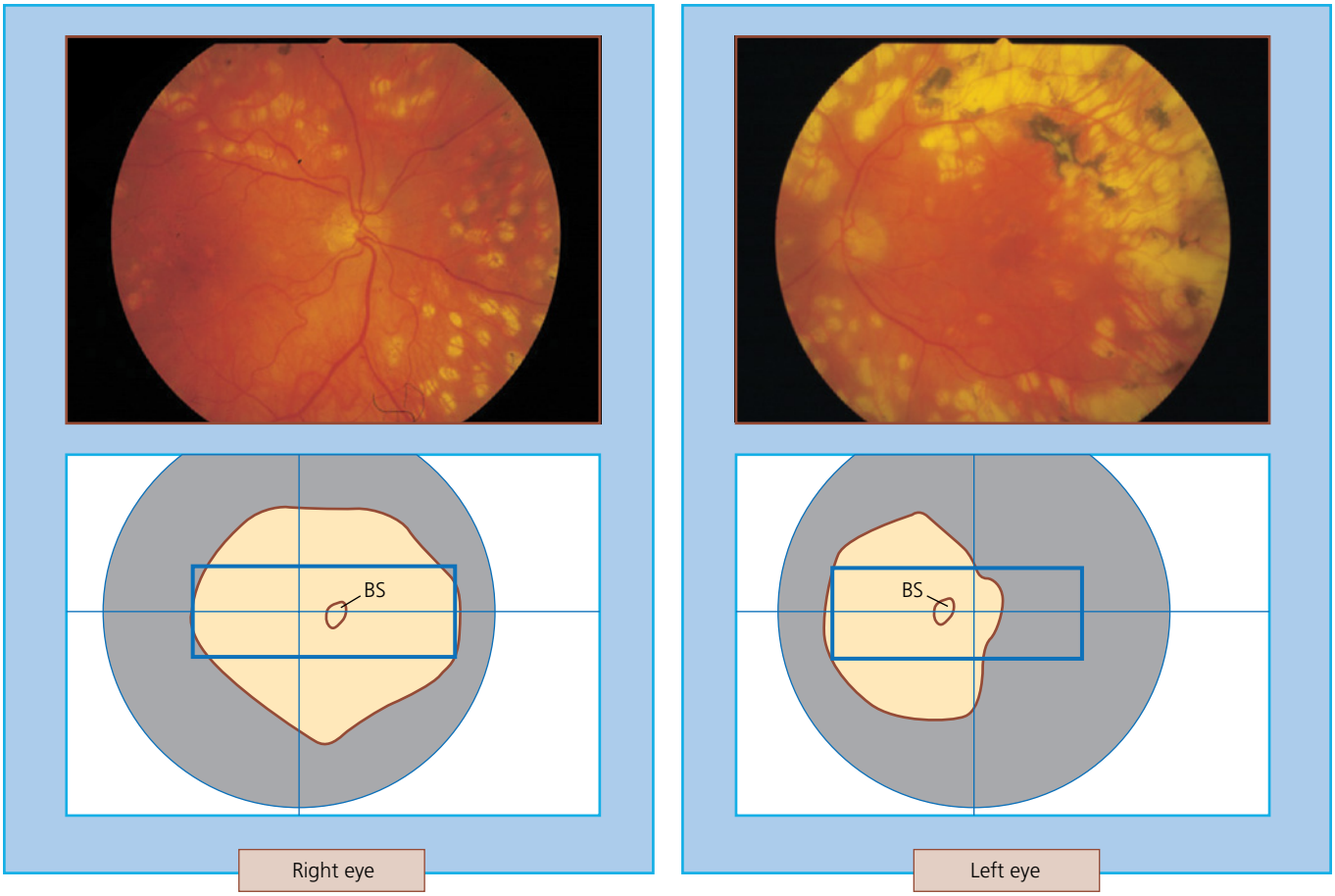

Figure 66.1 Visual field loss caused by photocoagulation. This 60-year-old man with diabetes needed extensive laser photocoagulation to the temporal retina of the left eye, causing nasal visual field loss that caused this eye to fail the standard test for driving. The right eye required less intensive laser treatment and the visual field was adequate for driving. BS, blind spot. Blue rectangle: minimum area recommended for safe driving. Source: Courtesy of D. Flanagan, Addenbrooke's Hospital, Cambridge, UK.

be told not to drive for at least two hours after the use of mydriatics. The driving regulatory authorities require perimetry to assess the visual fields of people who have had photocoagulation (Figure 66.1).

Statutory requirements for drivers with diabetes

In most high-income countries, drivers with insulin-treated diabetes are required by law to declare their diabetes to the relevant regulatory authority (in the UK this is the DVLA). The statutory requirements for ordinary and vocational (professional) driving licences vary considerably around the world, and in many countries no restrictions are imposed on insulin-treated drivers [30]; the national licensing authority should be contacted for details. Licensing restrictions have been criticized as being draconian and discriminatory against people with diabetes, but the civil rights of the person with diabetes have to be balanced against the need to safeguard public safety.

European driving licences

Ordinary driving licences (group 1)

The European Union (EU) member states and the UK all use the same classification for driving licences, but this is not applicable to other parts of the world. In the UK, the DVLA must be informed when a person with insulin-treated diabetes applies for, or renews, a driving licence, or if insulin dependence develops in a driver with diabetes. Failure to do this constitutes *concealment of a material fact*, which can incur a fine, but more importantly can invalidate a claim to the motor insurer; professed ignorance of the law is not accepted as an excuse. The onus to declare rests with the individual driver, but doctors who provide diabetes care, including general practitioners, have a responsibility to inform individuals with diabetes of this legal requirement, and should offer practical advice (Table 66.2). Drivers with diabetes who are treated with diet alone or with oral glucose-lowering medications do not have to notify the DVLA unless they have visual impairment or other diabetes-related problems that could affect medical fitness to drive. In the UK, a driving licence for a person with diabetes is period restricted, is usually issued for a maximum of three years, and is renewed after completion of a medical questionnaire. The DVLA requests further medical reports in some cases, and always when an applicant reports a medical problem that may seriously affect driving (e.g. recurrent hypoglycaemia). GLP-1 receptor agonists (given by injection) can be used without restriction, other than when prescribed in combination with a sulfonylurea for drivers with Group 2 (vocational) licences, when this must be notified to the DVLA and requires assessment of medical fitness to drive.

The member states of the EU have an agreed policy on restrictions on driving licences for people with insulin-treated diabetes, and these were changed after publication of the Third Directive on

driving licences (Annex III to European Directives 91/439/EEC and 2006/126/EC: Driving Licence Standards for Diabetes) in 2006 and implemented thereafter. The main provisions are as follows:

- The interval between regular medical reviews should not exceed five years; stricter rules are allowed.
- A driver must not experience more than one episode of severe hypoglycaemia within the preceding 12 months. This criterion raised concerns that it would lead to deliberate concealment of severe hypoglycaemia by insulin-treated drivers, which was strongly suggested by a Danish study [31] and in a further study in Denmark more than 20% of drivers admitted that they would under-report the frequency of severe hypoglycaemia [32]. No time was specified for when severe hypoglycaemia had occurred, so nocturnal episodes of severe hypoglycaemia during sleep were included. Several countries lobbied the European Commission to accept that severe hypoglycaemia during sleep should not hold the same weight in the assessment of fitness to drive as that occurring during waking hours. This led to the European Commission issuing Directive 2016/1106/EC, which amended the Third Directive on driving licences to exclude nocturnal events, and this legislation was implemented in January 2018. The rationale and appropriateness of the European regulations and this latest amendment can be questioned [33].
- A driver must not have impaired awareness of hypoglycaemia. No definition of this syndrome was given, and its interpretation was left to the discretion of individual states. The latest amendment changed the wording to *inadequate awareness of hypoglycaemia*. This altered terminology still fails to define precisely what this clinical problem represents, its nature and severity, and how it should be assessed and applied in relation to fitness to drive. In the UK it has been defined as 'an inability to detect the onset of hypoglycaemia because of a total absence of warning symptoms', which is rare in clinical practice.

Vocational driving licences (group 2)

It is extremely difficult to estimate the risk and likely outcome of a motor vehicle accident as many factors can be involved. Professional drivers have a much higher annual mileage than ordinary car drivers and a higher rate of driving mishaps overall. In the absence of scientific evidence, risk and hazard are gauged by the size of vehicle being driven, which is perhaps not unreasonable, given the potential consequences of a person losing control of a large heavy vehicle through hypoglycaemia. Before 2010 drivers with insulin-treated diabetes could not be issued with a Group 2 vehicle driving licence except in (undefined) *exceptional circumstances*, subject to (unspecified) authorized medical opinion, and were debarred from driving Group 2 vehicles, with the exception of C1 vehicles (3.5 to 7.5 t). However, in some European countries exceptional cases appeared to be the norm and the inconsistent application of EU regulations, inadequacy of assessment of medical fitness to drive, and lack of harmonization between states were very unsatisfactory. As these professional drivers were able to cross state borders and drive in countries with much stricter regulations for Group 2 driving licences, this was politically unacceptable. The EU regulations on driving have been relaxed and now allow all drivers with insulin-treated diabetes to apply for a Group 2 driving licence, provided they meet strict criteria including having no episodes of severe hypoglycaemia, having normal hypoglycaemia awareness, and undertaking frequent blood glucose monitoring at times relevant to driving (Annex III to European Directives 91/439/EEC and 2006/126/EC).

Oral anti-diabetes medication is not a bar to holding a vocational driving licence in the UK. In practice, however, many public transport companies restrict the employment of drivers with type 2 diabetes who take sulfonylureas; metformin or treatment with GLP-1 receptor agonists is not a contraindication, but medical assessment is normally necessary. Progression to insulin therapy usually terminates the employment of bus and train drivers. Taxi, ambulance, and police pursuit drivers are not covered by the statutory regulations. In the UK, taxi licences are issued by local authorities, which vary considerably in how medical fitness to drive is assessed, although many have now adopted Group 2 licensing standards. The employment of insulin-treated drivers in these other categories is determined by employers, who usually seek advice from occupational health physicians.

Driving outside Europe

Outside Europe, the regulations in different countries range from a complete ban to no restriction other than a medical examination for prospective or current drivers who require insulin [30]. Differences in approach between countries are influenced by the level of economic development and the prevalence of insulin-treated diabetes; many low- and middle-income countries impose no restriction on vocational driving licences for people with insulin-treated diabetes [30]. The American Diabetes Association has published a position statement with valuable practical recommendations about how to evaluate risks to driving associated with diabetes, and how these should influence licensing decisions in the USA [34]. Drivers with insulin-treated diabetes are prohibited from driving commercial motor vehicles across state borders in the USA, but within most states drivers with insulin-treated diabetes can drive commercial vehicles, with the exception of lorries transporting hazardous materials and passenger-carrying buses [35].

In most other countries, insulin treatment alone is targeted by legislation, even though hypoglycaemia can occur with other glucose-lowering drugs. A Canadian survey of crashes involving truck and commercial vehicle drivers with diabetes revealed an increase in risk for drivers with type 2 diabetes treated with sulfonylureas [36], the presumption being that unsuspected hypoglycaemia is a causal factor. Similarly, an insurance-based study in the USA of people with type 2 diabetes treated with (unspecified) non-insulin therapies showed that those who had made claims for hypoglycaemia had greater rates of motor vehicle incidents requiring hospital treatment [37], indicating that hypoglycaemia-related mishaps also occur in people with type 2 diabetes who are not being treated with insulin.

Aircraft pilot licences

Pilots with insulin-treated diabetes have been employed for several years by a Canadian commercial airline without any incidents, but in Europe pilots on insulin have not been allowed to fly commercial aircraft. However, the UK Civil Aviation Authority, in collaboration with the Republic of Ireland and the Austrian Aviation Authorities, is currently using an agreed protocol to certify individual pilots with insulin-treated diabetes to fly commercial aircraft, provided they meet strict medical fitness criteria, monitor glycaemic levels, and fly along with a co-pilot without diabetes [38]. Preliminary data have shown that the protocol is both practical and safe [39] and will merit

consideration by the European Aviation Safety Agency to allow certification of insulin-treated pilots in other European countries. Private pilot licences can be issued to individuals with diabetes treated with sulfonylureas (provided that they have a safety licence endorsement), but not with insulin. People with insulin-treated diabetes cannot work as air traffic controllers.

Employment

With a few provisos, people with diabetes can successfully undertake a wide range of employment. There remains some prejudice against people with diabetes, but employment prospects in the UK and many other countries have improved with the introduction of legislation that makes it unlawful to treat a disabled person less favourably.

The main concern when considering people with diabetes for employment is the risk to safety associated with the condition or its treatment. Employers often fail to make the crucial distinction between a *hazard* (something with the potential to cause harm) and a *risk* (the likelihood that such harm will occur). The potential problems of diabetes relevant to employment are the hazards of acute hypoglycaemia related to insulin and sulfonylureas, the lability of glucose levels, and the development of serious diabetes-related complications that may affect ability to work or interfere with performance at work.

Employment is generally restricted where hypoglycaemia could be hazardous to the worker with diabetes, their colleagues, or the general public. Employment-related issues, however, are not confined to people with type 1 diabetes. The rising prevalence of type 2 diabetes in the population of working age, along with the increasing use of insulin, has become an issue for occupational health assessment. Access to employment may be limited through discriminatory employment practices and restrictions posed by companies (rather than by legislation) because of perceived problems associated with diabetes or to job-sensitive issues related to the potential risks of hypoglycaemia or to visual impairment. Diabetes can also affect employment through increased sick leave and absenteeism and by adversely influencing productivity. Diabetes in general has a negative long-term influence on the economic productivity of the individual; health-related disabilities can cause work limitations, especially in older employees in whom early retirement is more common on medical grounds.

A prospective survey in Edinburgh of 243 people with insulin-treated (mainly type 1) diabetes in full-time employment found that hypoglycaemia occurred uncommonly at work (14% of all severe episodes) and had few adverse effects [40]. The study cohort, however, may have been subject to selection bias in terms of occupational diversity and many had suboptimal glycaemic levels; surprisingly few participants had impaired awareness of hypoglycaemia. An internet survey of the effects of non-severe hypoglycaemia in people with type 1 diabetes and type 2 diabetes in employment has suggested that work time and productivity are lost by around one in five people when hypoglycaemia occurs at work, though such an uncontrolled study may be open to overestimation of the magnitude of the problem [41].

For some occupations (e.g. train drivers) any risk of hypoglycaemia is considered unacceptable. Elsewhere, the case for employment restrictions may be less clear-cut. Jobs that restrict the employment of workers with insulin-treated diabetes are listed in Table 66.3. People treated with insulin are not usually permitted to work alone in isolated or dangerous areas, or at unprotected heights. Shift work is not necessarily a contraindication: one study in a car assembly plant found no difference in glycaemic levels between day- and night-shift workers with diabetes, although glycaemia deteriorated if shift rotas were changed frequently [44].

Table 66.3 Forms of employment from which people with insulin-treated diabetes may be excluded in the UK.

Vocational driving
Drivers of passenger-carrying vehicles (PCVs)
Drivers of locomotives and underground trains
Professional drivers, such as chauffeurs (depends on employer)
Taxi drivers (variable; depends on local authority policy)
Civil aviation
Commercial pilots and flight engineers (licensing may be allowed with strict operational restrictions and in-flight testing regimens)
Aircrew (as above)
Air-traffic controllers (as above)
National and emergency services
Armed forces (army, navy, air force)
Police force
Fire brigade or rescue services (some exceptional cases)
Merchant navy
Prison and security services
Dangerous areas for work
Offshore: oil rigs, gas platforms
Moving machinery
Incinerators and hot-metal areas
Work on railway tracks
Coal mining
Heights: overhead lines, cranes, scaffolding

Source: Data from Waclawski 1989 [42] and Waclawski and Gill 2013 [43].

In one British survey, the prevalence of diabetes in the workforce was 7.5 per 1000, including a lower than anticipated rate of 2.6 per 1000 for people treated with insulin [42]. Employment is generally debarred in the armed forces, emergency work such as firefighting, civil aviation, jobs in the offshore oil industry, and many forms of commercial driving [42]. Workers with diabetes seldom conceal their medical condition from their employers, and any blanket policy that debars workers with diabetes from a specific occupation may be inappropriate or even discriminatory. Individual assessment is crucial, as employment regulations may not differentiate between different types and treatments of diabetes. Some bureaucratic regulations have been successfully challenged on medical grounds: for example, active firefighters in the UK and a US air traffic controller were reinstated following appeals against dismissal.

In some cases, entering or persevering with a specific occupation may not always be in the individual's long-term interests (e.g. with the advance of disabling complications). This is clearly a difficult issue, which may require sympathetic medical counselling because of possible repercussions on the individual's income, self-esteem, future quality of life, and the financial support of dependants.

Unemployment, sickness, and diabetes

According to a British survey, employers do not generally believe that diabetes *per se* limits employment prospects, because most workers with diabetes have few medical problems and can tackle a wide range of occupations [45]. Discrimination by employers, however, may affect hiring practices. Some British and Dutch surveys

reported no apparent excess of unemployment among people with diabetes compared with the general population [46–49], but other studies in the UK [50, 51] found that relatively more people with diabetes were not earning because of inability to work, intercurrent illness, early retirement, or by being housewives. Although in many cases there was no apparent reason why an individual with diabetes could not obtain employment [51], depressive illness is strongly associated with unemployment and difficulties with work performance [52]. Adolescents with diabetes appear more likely than their peers without diabetes to lose jobs, or to fail to follow their desired occupation or cope with shift work [53]. Reduced employment and income in workers with diabetes in North America have been related to work disability [54], which was seven times more common than among siblings without diabetes and was mainly related to diabetes-related complications [55], and was associated with lower employment income [43, 56]. Sickness absence rates among employees with diabetes are moderately to substantially higher than in workers without diabetes [57–60], which has economic and social consequences. Workers with insulin-treated diabetes and optimal glycaemic management had fewer sickness absences than those with suboptimal management, but HbA_{1c} is not a good index of capacity to work [61]. Diabetes reduces employment and contributes to work loss through absenteeism and health-related work limitations in the workplace [62]. A systematic review of type 2 diabetes and employment showed that it reduces the ability of an individual to work, principally in terms of absenteeism, loss of productivity, and early retirement, and exerts a significant burden on the workforce [63].

Prison and custody

Imprisonment and short-term custody are unusual but troublesome life situations that can interfere with the management of diabetes. Hypoglycaemia can occur if food is withheld after arrest and may be confused with intoxication by alcohol or drugs. Diabetes is generally managed badly in prison because of the unsuitability of prison diets, lack of exercise, and the practical difficulty of using some insulin regimens (e.g. basal bolus); also, self-monitoring may be prohibited, and glucose to treat hypoglycaemia may be unavailable during long lock-up periods. Most prison medical personnel have no specialist knowledge of diabetes and there may be no access to specialist supervision during custody.

Some prisoners with diabetes deliberately manipulate their treatment (e.g. by omitting insulin to induce ketoacidosis to have themselves removed to hospital, which arguably offers a more amenable environment [64]). By contrast, treatment of intercurrent illness may be delayed by prison staff, who think that the prisoner is 'misbehaving'.

In some cases, withdrawal of alcohol, better diet, and weight loss may actually improve glycaemic levels while in prison, and structured diabetes care can be provided effectively by an attending specialist physician [65, 66]. Facilities for people with diabetes in police custody are generally limited, with an inability to measure blood glucose, treat diabetic emergencies, or provide insulin and appropriate meals [67]. A Scottish liaison initiative between a specialist diabetes department and the local police force identified and successfully addressed deficiencies in its custody facilities, including the provision of glucose monitoring equipment and the training of police staff [67]; this has been assisted by the development of a forensic nursing service.

Insurance

In many societies, insurance is viewed as essential to protect individuals and their families from the financial risk of unexpected events or illness, and insurance is often necessary to secure a financial loan, as for house purchase. This chapter does not address how models of healthcare insurance are provided in different countries, an example being Medicaid in the USA, or how expansion of that insurance system has influenced diabetes-related biomarkers [68]. Different healthcare insurance systems may limit reimbursement or ration access to specific medications, glucose monitoring equipment, or sophisticated technologies to treat diabetes.

People with diabetes are sometimes refused insurance or have to accept higher premiums and limited coverage, because the disorder is associated with reduced life expectancy, the risk of complications, and greater use of healthcare services. Several factors are important for insurance underwriting, including the severity and duration of the diabetes, and the existence of diabetes complications and other concurrent medical disorders. It is reasonable for an insurer to be cautious in dealing with applicants who have suboptimally managed long-standing diabetes and established complications.

There is wide variation in insurance terms and premiums among different European countries [69], in the USA [70], and even within the UK [71], which suggests that insurers work from assumptions about diabetes rather than using scientific evidence from actuarial studies. The presence of type 1 diabetes may be the only factor considered by insurers [70], and many still base potentially discriminatory decisions on outdated information that reflects the poor outcome of diabetes diagnosed and treated decades ago. There are no standardized guidelines, nor is there any uniformity in the approach to diabetes and insurance [71], although risk classifications for life insurance have been published [72]. Some companies do not accept applicants with diabetes, while others do so without financial penalty. People with diabetes seeking insurance cover should therefore request quotations from several companies and should be supported by a medical assessment from a physician who is competent in the specialty. Many national patient organizations have negotiated favourable terms with insurance brokers and will provide details on request.

The prognosis of people with diabetes (particularly type 1 diabetes) has improved considerably during the last 50 years, and the impact of this on life insurance for people with type 1 diabetes has been analysed in Scandinavia [73]. In the last 30–40 years, median life expectancy has increased by over 15 years, largely because of substantial reductions in diabetic nephropathy. It has therefore been suggested that life insurance in type 1 diabetes should focus entirely on the risk of developing diabetic nephropathy [74], and a model to calculate insurance terms has been proposed, based on current age, age at diagnosis, sex, presence of nephropathy or proliferative retinopathy, and other pre-existing disease [73]. As the risk of developing new nephropathy falls after 25 years of diabetes, all people who reach the age of 50 years without nephropathy should have their insurance premium reduced. This approach has been adopted by most insurance companies in the Nordic countries, and by some in other European countries. To avoid penalizing people with diabetes, there must be regular updating of mortality and life expectancy data, and this information must be transmitted to actuarial advisers and insurance underwriters.

People with diabetes also face higher premiums for accident insurance, which is unjustified because there is no evidence that they have more accidents or permanent disability than the general population [75]. Neither is there any rationale for higher motor insurance premiums [70, 71, 76], particularly for those not treated with insulin, because no excess in road traffic accidents has been demonstrated. A US study of the insurance cost of employees with diabetes showed that while healthcare expenditure was three times higher than all healthcare consumers, it was not more expensive than other chronic illnesses such as heart disease, asthma, and cancer [77].

Diabetes must always be disclosed to the insurer: concealing the diagnosis constitutes the withholding of a material fact, which nullifies the contract with the insurer and thus the insurer's liability in the event of a claim.

Alcohol

Many people enjoy drinking alcohol and diabetes should not be a barrier to social drinking. Moderate alcohol consumption not only reduces the risks of developing type 2 diabetes, but improves metabolic management and restricts diabetes-related complications. By contrast, alcohol can promote hypoglycaemia and chronic excessive consumption may be deleterious both to long-term diabetes management and to general health. Patterns of alcohol consumption vary substantially across the world. Consumption of excess alcohol is linked in some countries to social deprivation and so it might be presumed that there would also be a strong link to type 2 diabetes. However, in the USA for example, alcohol consumption in older people with diabetes appears to be lower than in individuals without chronic health problems, although approximately 4.5% of older people with diabetes still drink to excess [78]. In adolescents with type 1 diabetes, alcohol consumption is probably similar to that in peers without diabetes [79], but some studies have reported higher levels of overall consumption and /or greater binge drinking than in adolescents without type 1 diabetes [80, 81].

Alcohol consumption and risk of diabetes

Chronic high consumption of alcohol can predispose to the development of secondary diabetes. Alcohol has a direct toxic effect on the pancreas, resulting in both acute and chronic pancreatitis. Diabetes complicates about 45% of cases of chronic pancreatitis (Chapter 23). Insulin treatment is usually required to manage hyperglycaemia in people with chronic pancreatitis, although diabetic ketoacidosis is rare. This may be because the pancreatic damage also destroys the α cells that secrete glucagon, which is an essential factor in ketogenesis (Chapters 8 and 41). Insulin therapy can be particularly challenging in this situation, as many individuals with alcohol-related chronic pancreatitis have chaotic lifestyles, with poor diet and ongoing excess alcohol consumption. A heavy alcoholic binge, with concomitant low food intake, can result in alcoholic ketoacidosis.

By contrast, modest alcohol consumption appears to protect against type 2 diabetes, reducing risk by up to 30% [82, 83]. A J-shaped relationship has been observed between alcohol consumption and risk of type 2 diabetes (Figure 66.2). Moderate alcohol consumption is associated with enhanced insulin sensitivity, which may in part explain the relationship. The pattern of drinking behaviour also appears to be important, with binge drinking associated with an increased risk of type 2 diabetes [84].

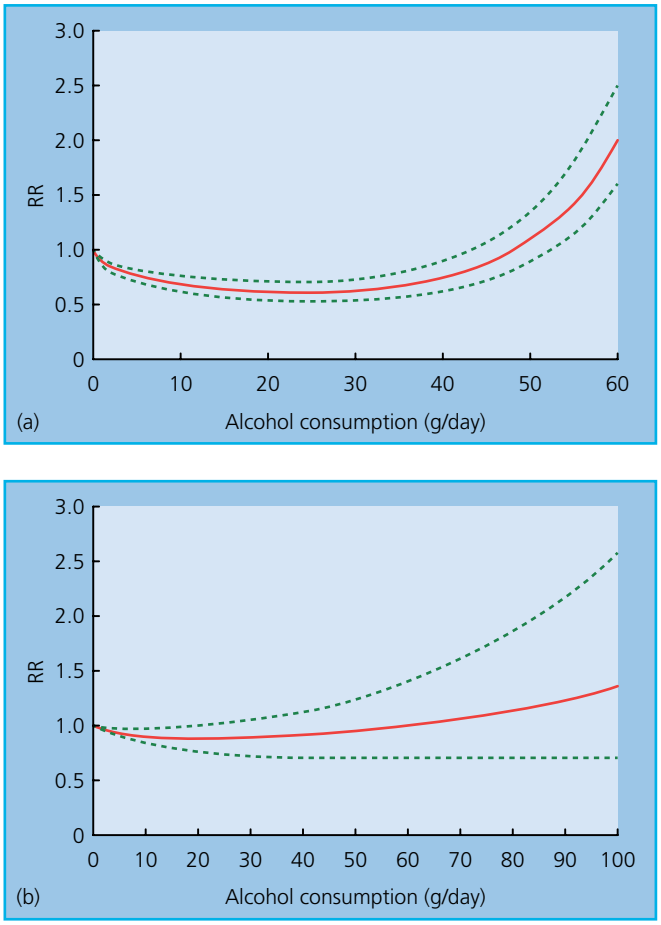

Figure 66.2 Relationship between alcohol intake and risk of diabetes in (a) women and (b) men. Solid lines represent the pooled and fitted relative risk (RR) estimates and the dotted lines are the 95% confidence intervals. Source: Pietraszek et al. 2010 [84]. Copyright 2010 Elsevier.

Alcohol and glycaemic levels

Alcohol consumption in a real-life setting can have very variable effects on blood glucose [85]. In part, this is because the nature of alcohol consumption can vary considerably, ranging from a glass of wine with a meal to an episode of excessive binge drinking. Alcoholic beverages vary significantly, not only in their content of alcohol, but also in their physical volume and carbohydrate and glucose content. Some forms of alcoholic drinks, such as white wine, may be more prone to cause hypoglycaemia, while others, such as red wine, may be more prone to cause hyperglycaemia [85]. Patterns of food ingestion with alcohol also vary substantially and alcohol ingestion may be accompanied by the use of one or more recreational drugs.

Hypoglycaemia

Ethanol has marked metabolic effects on the liver, which metabolizes over 90% of an alcohol load. Gluconeogenesis is suppressed, even at blood alcohol levels that are not usually associated with intoxication [86–88], while the processes of recycling carbon as glucose and lactate between hepatic gluconeogenesis and muscle glycolysis [87] and fatty acid oxidation are also inhibited by alcohol. Thus, alcohol has the potential both to predispose to hypoglycaemia and to inhibit glucose recovery. In individuals without diabetes, total hepatic glucose production is not reduced by alcohol, despite the inhibition of gluconeogenesis [88], and alcohol-induced

hypoglycaemia only occurs if hepatic glycogen stores are already depleted; for example, by fasting for at least 36 hours [89].

In people with diabetes, alcohol consumption may impede recovery from insulin-induced hypoglycaemia. This effect is often delayed, occurring up to 24 hours after alcohol ingestion, and may occur during the night or the following day [90]. Those with a deficient glucagon response to hypoglycaemia (Chapter 40) may be at greater risk, because they are unable to increase hepatic gluconeogenesis. The signs of hypoglycaemia may be missed or mistaken for those of alcohol intoxication by the individual or by observers, and even moderate alcohol consumption increases the cognitive impairment that occurs during hypoglycaemia [91]. People with insulin-treated diabetes should be advised not to drink *any* alcohol before driving.

Overall, alcohol is an important contributory factor to many episodes of hypoglycaemia in people with diabetes, an estimated 20% in one study [92]. Hypoglycaemia-induced brain damage is rare, but when it occurs it is often preceded by excessive alcohol consumption, which presumably promotes protracted neuroglycopaenia. Severe hypoglycaemia caused permanent neurological damage after binge drinking in five alcoholic people with insulin-treated diabetes, two of whom died [93].

Hyperglycaemia

Excessive alcohol consumption is associated with central obesity [94], which may be a consequence of the adverse lifestyle factors that tend to accompany high alcohol intake. It should also be noted that alcohol provides 7 kcal energy/g (1 unit = 10 g alcohol) in an easily consumable form and can therefore provide a substantial caloric intake, particularly as beer and lager. This is a commonly overlooked source of calories in middle-aged men with type 2 diabetes and obesity, who are having difficulty in achieving weight loss by dietary means. The caloric content of spirits is much lower but may be augmented by adding sugar-rich mixers to drinks. Low-carbohydrate beers and lagers have been marketed as being suitable for people with diabetes, but should not be recommended because of their high alcohol content.

Heavy drinking has also been linked with poorer medication taking, outpatient follow-up, and self-blood glucose monitoring [95, 96]. Despite this, and the association with increased central obesity, excessive alcohol consumption does not appear to be associated with worse long-term glycaemia. Indeed, in most studies there is a linear inverse relationship between glycaemic levels and alcohol consumption [84, 97]. However, people with very heavy alcohol consumption tend to be under-represented in such studies.

Alcohol and the complications of diabetes

Moderate alcohol consumption in people with type 2 diabetes is associated with a 35% reduction in total mortality compared with non-drinkers (i.e. a similar magnitude to the effect of moderate alcohol on the risk of developing type 2 diabetes [98]) (Figure 66.3). These favourable effects of alcohol consumption may be a consequence of enhanced insulin sensitivity, lower blood pressure, and favourable changes in lipids and haemostatic factors [84]. These observations again do not include data on substantive numbers of very heavy drinkers, and it is well established that excessive alcohol consumption increases serum triglyceride concentrations in susceptible individuals and raises blood pressure; excess alcohol consumption is an important cause of hypertension failing to respond to treatment (Chapter 47). In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) trial, mortality and risk of cardiovascular events were indeed higher in people with type 2 diabetes who drank more than the UK-recommended limits [99].

With regard to microvascular complications, a J-shaped relationship is observed between risk and alcohol consumption [100]. Moderate consumption (30–70 g/wk) is associated with a 40% reduction in risk of proliferative retinopathy and neuropathy in type 1 diabetes, and over 60% reduction in risk for macroalbuminuria. Conversely,

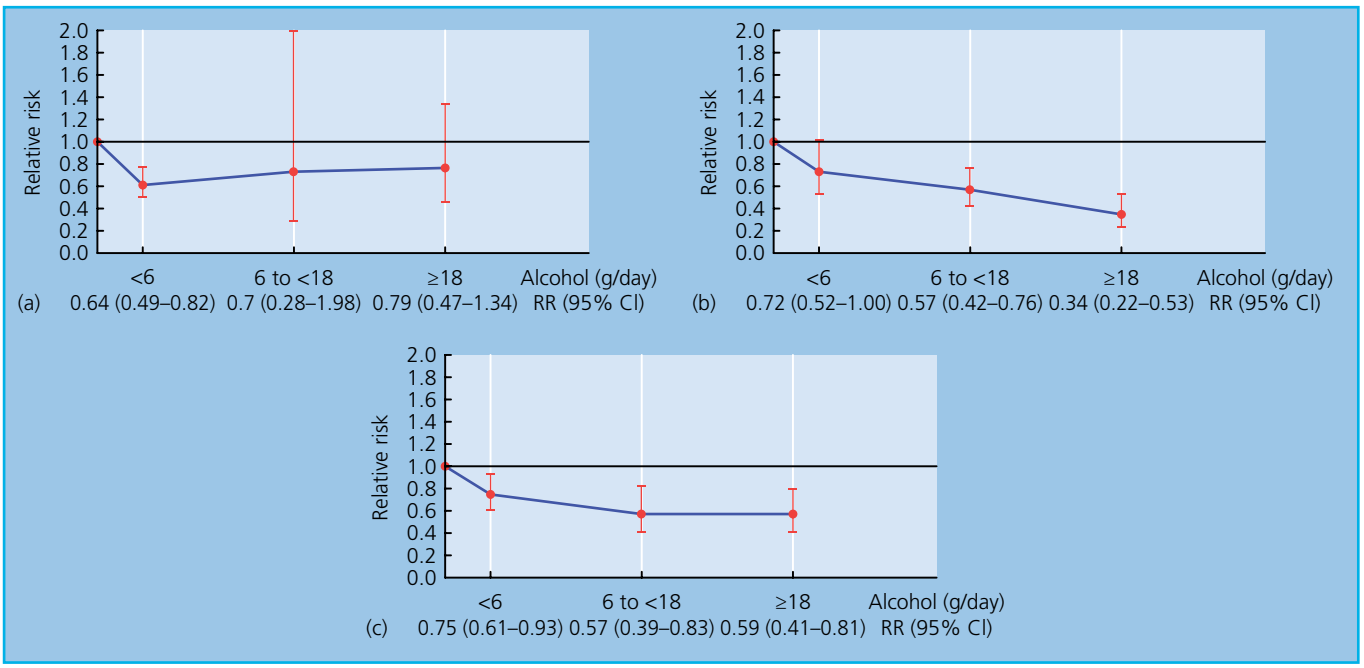

Figure 66.3 Pooled relative risk estimates (with 95% confidence intervals) of (a) total mortality; (b) coronary heart disease mortality; and (c) coronary heart disease incidence for three alcohol consumption categories, with non-drinkers as the reference. Source: Koppes et al. 2006 [98]. Reproduced by permission of Springer.

Table 66.4 General advice on alcohol for people with insulin-treated diabetes.

Small to moderate amounts of alcohol taken with a meal should not have a major effect on blood glucose levels
Larger amounts of alcohol can make blood glucose rise or fall
Avoid drinking on an empty stomach, as it may let the alcohol be absorbed more quickly and cause a hypo (low glucose)
Always ensure you have taken some carbohydrate before and after drinking alcohol
Check your blood glucose and consume a carbohydrate snack before going to bed.
A severe hypo can occur with larger quantities of alcohol, especially if insufficient carbohydrate has been eaten
A hypo may be delayed and occur up to 16 h after heavy drinking, so in addition check your glucose levels regularly during the next day
A hypo can be confused with being drunk. Tell people you have diabetes and wear or carry some form of diabetes identification
All types of alcoholic drinks contain calories and may contribute to weight gain
Low-carbohydrate beers and cider generally have a higher alcohol content
Low-alcohol wines are often higher in sugar than ordinary ones
Mixer drinks should be diet or sugar-free, such as diet tonic water and diet cola
Drinking and driving should be avoided

chronic excessive consumption of alcohol in people with diabetes is associated with peripheral neuropathy and exacerbation of neuropathic symptoms, erectile dysfunction, and increased risk of foot ulceration [101]. This may be in part a direct toxic effect of alcohol on the nervous system, though acute alcohol intoxication also impairs erectile function, while poor self-care and hygiene behaviours may contribute to the association between alcohol and foot ulceration.

Recommended alcohol intake

Overall, reflecting many of these factors, studies on the effects of blood glucose in diabetes are very heterogeneous and it is difficult to draw firm conclusions. This is particularly the case because observational studies generally do not discuss the actions taken by individuals to alter their diabetes treatment to reduce the risk of hypo-/hyperglycaemia. However, it is probably reasonable to conclude that consumption of low to moderate amounts of alcohol does not have a major negative effect on glycaemia in diabetes [102], but it may increase glycaemic variability in type 1 diabetes [103] and so caution is required. Large binges of alcohol and/or chronic consumption of excess alcohol are likely to have negative short- and long-term consequences. Recommendations for average alcohol intake in people with diabetes are, therefore, comparable with advice given to the general population; that is, women with diabetes should drink no more than 2 units of alcohol per day and men no more than 3 units. General advice for people with insulin-treated diabetes regarding alcohol is summarized in Table 66.4.

Recreational drugs

Use of recreational drugs is a serious problem in the general population and can pose particular difficulties for people with diabetes [104]. The main traditional classes of drugs involved are cannabis, amfetamine-type stimulants (including ecstasy), cocaine, and opiates, with cannabis being the most commonly used drug by far. In recent years, numerous new psychoactive drugs have been developed to mimic the effects of the main illicit drug classes, but to remain legal; they were previously known as 'legal highs'. The rapid proliferation of these chemicals is a challenge for authorities, not least in determining which should be subject to legal controls. There are four main categories of new psychoactive drugs:

- Synthetic cannabinoids (e.g. Spice, Black Mamba, and Clockwork Orange).
- Stimulant-type drugs that mimic drugs like amfetamine, ecstasy, and cocaine (e.g. mephedrone, benzylpiperazine [BZP]).
- Tranquillizer-type drugs that mimic the effects of drugs like benzodiazepines (e.g. etizolam, pyrazolam).
- Hallucinogenic drugs that mimic the effects of drugs like lysergide (LSD) (e.g. 25i-NBOMe, Bromo-Dragonfly).

Other legal drugs are also being used increasingly for their psychoactive properties, including nitrous oxide and salvia.

Regulation

In the UK, drugs that are associated with dependence or misuse are regulated under the Misuse of Drugs Act 1971. This Act specifies a classification system for drugs according to harm associated with misuse and specifies controls over manufacture, supply, and possession (Table 66.5). The list of drugs within each class can be amended by order of the Home Secretary. The Misuse of Drugs Regulations 2001 define the classes of individuals who are authorized to supply and possess controlled drugs and lay down the conditions under which these activities may be carried out. Drugs are classified under five schedules, which specify the requirements governing import, export, production, supply, possession, prescribing, and record keeping. Cannabis and LSD are classified as Schedule 1 (drugs with no therapeutic value), while opiates, cocaine, and amfetamine are classified as Schedule 2 (drugs that can be used if appropriately prescribed) and are subject to full controlled drug requirements.

Table 66.5 Classification of controlled drugs.

Class A includes:[a]
Cocaine
Diamorphine (heroin)
Methadone
Methylenedioxymethamfetamine (MDMA, ecstasy)
Morphine
Opium
Pethidine
Methamfetamine (crystal meth)
Class B includes:
Oral amfetamines
Barbiturates
Codeine
Cannabis
Synthetic cannabinoids
Synthetic cathinones
Ketamine
Class C includes:
Most benzodiazepines
γ-Hydroxybutyric acid (GHB)
Cathinone (khat)
Zolpidem
Androgenic and anabolic steroids

[a] Includes Class B substances when prepared for injection.
Source: Data from UK Misuse of Drugs Act 1971.

New psychoactive drugs are regulated in the UK by the Psychoactive Substances Act 2016. This Act makes it an offence to produce or supply these drugs, but possession is not an offence. However, some synthetic cannabinoids, such as Spice, have been classified as Class B under the Misuse of Drugs Act.

Prevalence of recreational drug use

On a global scale, it is estimated that in 2018 between 5.4% of the world population aged 15–64 years (269 million people) had used recreational/illicit drugs at least once in the preceding year [105]. In England and Wales in 2019–2020, 9.4% of adults aged 16–59 years had taken a recreational drug in the preceding year, but this figure rose to 21% in adults aged 16–25 years [106]. Around 70% of use of new psychoactive drugs was by individuals aged 16–24 years and approximately one-third of adults had used recreational drugs at least once in their lifetime [106]. Trends in recreational drug use have changed over the years, with a decline in the use of LSD, amfetamine, and solvents and an increase in the use of cocaine, nitrous oxide, and new psychoactive drugs, particularly associated with the night-club and rave culture. Cannabis and powder cocaine remain the most commonly used illicit drugs in the UK.

Specific data about the use of recreational drugs by people with diabetes are sparse. Two uncontrolled questionnaire surveys of young adults with type 1 diabetes, one from the USA and one from the UK, have reported a similar prevalence and pattern of recreational drug use to that observed in the general population [107, 108]. In the UK survey, approximately 30% of respondents had used recreational drugs, with cannabis (28.2% of respondents), amfetamine-type stimulants (13%), and cocaine (12%) being used most commonly [108]. Many (15% of respondents) used more than one drug. Another questionnaire study in the USA in younger people with type 1 diabetes (aged 12–20 years) reported lower rates of recreational drug use (23.4% of respondents), with cannabis use overwhelmingly being the most used drug [109]. A report from Chile suggested that use of recreational drugs was lower in school-aged adolescents with type 1 diabetes than in the general population (9.6% vs 22.2%), although this difference disappeared during later years at school [110]. In all studies examining the prevalence of recreational drug use, under-reporting by respondents is highly likely, related in part to fear of retribution.

Impact of recreational drug use on diabetes

In the Diabetes UK Cohort Study, acute metabolic complications (diabetic ketoacidosis and, to a lesser extent, severe hypoglycaemia) were the most common causes of death in adults with type 1 diabetes under the age of 30 years, closely followed by accidents and violence [111]. In that study, a history of previous drug abuse was associated with a nearly sixfold increased risk of death from acute complications. More than 50% of young adults presenting with diabetic ketoacidosis to a tertiary referral hospital admitted to using recreational drugs; a history of recreational drug use was volunteered by only 20% on initial questioning [112]. Drug misuse has also been identified as a major cause of death in young people with type 1 diabetes [113]. Substance abuse co-occurring with mental illness is associated with a particularly high mortality [114]. There are relatively few data on the effects of new psychoactive drugs on diabetes [115].

Intravenous drug abuse

Recreational drug use often disrupts normal lifestyle and a person with diabetes may abandon the daily routine of regular meals and insulin injections. Recreational drug use may also be only one aspect of a chaotic lifestyle associated with other high-risk behaviours. This can result from the use of any recreational drug, but intravenous drug abuse (particularly of opiates, but also amfetamines) is particularly damaging and is strongly associated with poor social support, criminality, and mental illness. Intravenous drug use is uncommon in people with diabetes (as it is in the general population), but is associated with omission of insulin therapy, frequent admissions to hospital, and high mortality, both from diabetic ketoacidosis and from deliberate or accidental opiate overdose [116]. Unsurprisingly, intravenous drug abusers with diabetes may also present with complications related to the route of drug administration: deep venous thrombosis and abscesses at groin or limb injection sites. Intravenous drug abusers often default from outpatient clinic attendance (this may be associated with imprisonment) and maintaining contact with such individuals is usually difficult.

Cocaine, amfetamines, and other stimulants

Cocaine and amfetamine-type stimulants can have dramatic effects on the cardiovascular system through activation of the sympathetic nervous system [117]. Cocaine is a sympathomimetic that inhibits reuptake of norepinephrine and dopamine at sympathetic nerve terminals. Amfetamine and ecstasy potentiate the release of norepinephrine, dopamine, and serotonin from the central and autonomic nervous systems. Cocaine toxicity may be potentiated by cannabis, while amfetamine toxicity is enhanced by alcohol. Drug-induced sympathetic activation leads to tachycardia, vasoconstriction, and hypertension. Myocardial ischaemia and infarction, supraventricular and ventricular tachyarrhythmias, and severe hypotension can all occur. Prolonged use can result in a dilated cardiomyopathy. The sympathetic activation produced by these drugs antagonizes the action of insulin and use of stimulants such as cocaine and mephedrone has been identified as a risk factor for diabetic ketoacidosis [118, 119]. The risk of diabetic ketoacidosis may be increased by the omission of insulin due to behaviour change induced by these substances and/or to avoid the potential risk and embarrassment of hypoglycaemia.

Ecstasy is also associated with severe hyponatraemia, secondary to a combination of inappropriate secretion of antidiuretic hormone, polydipsia, and a proximal renal tubulopathy [108, 112].

Ketamine

Ketamine acts as an N-methyl-D-aspartate receptor antagonist and so reduces excitatory neurotransmission. It induces a state of relaxation and dissociation ('K-land'), but hypertension, hyperthermia, tachycardia, and seizures can occur in severe intoxication. Ketamine can precipitate diabetic ketoacidosis, with a metabolic acidosis that is severe and disproportionate to the degree of ketosis. It can also be associated with metabolic acidosis without ketoacidosis and rhabdomyolysis [112].

Cannabis

Cannabis plants produce a whole array of cannabinoids; tetrahydrocannabinol (THC) is the major natural cannabinoid with psychoactive effects. The endocannabinoid system in humans is important in the regulation of weight and food intake. Cannabis is not known to have major effects on glucose metabolism (other than by stimulating weight gain), but its effects on the central nervous system may increase appetite, affect behaviours with regard to insulin and other diabetes medications, and impair recognition of hypoglycaemia. Use of cannabis in low doses is associated with sympathetic activation and tachycardia; at high

doses, parasympathetic activation may predominate, resulting in bradycardia and hypotension. In the absence of any structural heart disease, these effects are usually well tolerated.

A wide variety of cannabis extracts and synthetic cannabinoids exist, some of which have little or no psychoactive effects. Many of these are purported to have health benefits, but with very little scientific evidence to support these claims. Δ9-tetrahydrocannabivarin (THCV), a non-psychoactive cannabinoid, reduces blood glucose in type 2 diabetes [120]. Leaving aside its potential therapeutic use in the future, this acts a reminder that cannabis extracts and synthetic cannabinoids may have differing degrees of agonism and antagonism on cannabinoid receptor subclasses and thus have differing effects on diabetes.

Nitrous oxide

Nitrous oxide is used in the food industry as a foaming and whipping agent. It is cheap and legally available in many outlets in cannisters and balloons. It is increasingly being used as a recreational drug. Inhalation provides a very rapid onset of euphoria and disinhibition, which in turn is of very short duration and is usually not associated with a hangover effect. In theory, nitrous oxide should not pose any particular issues in relation to diabetes, other than a transient reduction in the ability to recognize and treat hypoglycaemia. It is associated with relative hypoxaemia; this is not a problem in healthy individuals, but could be harmful in individuals with cardiovascular disease.

Hypoglycaemia

While the association between recreational drug use and diabetic ketoacidosis is well established, there are few data suggesting any association with hypoglycaemia. Such drugs, however, are often taken in conjunction with alcohol and may be associated with poor oral intake of carbohydrate, both of which will increase the risk of hypoglycaemia. Moreover, amfetamine-like stimulants can induce frenetic behaviour at night clubs and raves, which can induce hypoglycaemia in people treated with insulin [121]. The hallucinatory, or central nervous system, depressant effects of recreational drugs may impair an individual's ability to recognize and treat hypoglycaemia. Furthermore, the sympathomimetic effects of cocaine and amfetamine-type stimulants may mimic the autonomic signs and symptoms of hypoglycaemia.

Advice on recreational drug use in diabetes

Recreational drugs cause significant morbidity and are hazardous for people with diabetes. Their dangers must be emphasized to people with type 1 diabetes (particularly teenagers and young adults), but advice must be given in a sensitive and non-judgmental manner. When exposed to recreational drugs and alcohol, modest reductions in insulin dosage and regular consumption of carbohydrate-based snacks or non-alcoholic sugary drinks are required, particularly if strenuous dancing is to be undertaken. In such situations, significant dehydration can occur, and water should be regularly consumed. Music festivals are increasingly popular, and the ready availability of alcohol and recreational drugs poses additional risks due to the more prolonged nature of the events over several days, poor sanitation, limited food choices, and the potential for significant peer pressure. People with type 1 diabetes attending such events should be advised of the potential hazards and the need to moderate consumption of alcohol and recreational drugs, while maintaining a regular intake of food and non-alcoholic beverages. Regular glucose monitoring should be strongly advised, although the reality is that frequent monitoring is likely to fall by the wayside during the excitement of the event.

Travel

Diabetes should not be regarded as a bar to short- or long-distance travel, although careful planning may be required to avoid metabolic disturbances and other problems of diabetes that could have particularly serious consequences away from home. Diet and an adequate fluid intake may be disrupted while travelling or staying abroad, and local differences in climate, food, endemic diseases, and medical facilities may compromise diabetes control. Blood glucose levels should be monitored frequently during travel and holidays, and people with diabetes must be able to take a pragmatic approach to deal with contingencies (e.g. loss of insulin, delays during travel) that could perturb their diabetes. Occasionally, specific diabetes complications or other medical disorders such as uncontrolled hypertension or ischaemic heart disease can jeopardize health and safety during travel and periods away from home.

Preparation for travel

Personal identification

Travellers with diabetes should carry a doctor's letter stating the diagnosis and treatment, and ideally some other form of identification such as medical identification jewellery or tags (these contain personalized medical information and are recognized worldwide). These should also allay the suspicions of airline security, immigration, and customs officials who discover syringes and drugs in luggage. Many national diabetes associations provide an identification card that shows the person's photograph, doctor's name, and contact telephone number.

If a prolonged stay abroad is intended, it is useful to carry a prescription letter listing all medications (with generic names, as brand names often vary between countries), insulin-injection devices, and blood-testing items.

Insurance and medical care abroad

Comprehensive medical insurance is essential to cover accidents and illness that require medical assistance, and loss of medical equipment and drugs. The insurance policy must cover diabetes and other pre-existing medical conditions, as claims relating to these may otherwise be rejected. Most travel policies contain exclusions and diabetes is frequently listed; a person with diabetes may not be covered for conditions such as a stroke or myocardial infarction for which diabetes is a recognized risk factor. When appropriate, insurance must be adequate to cover any dangerous sporting activities (when hypoglycaemia could be particularly hazardous), and the costs of emergency air transport home in the event of a serious accident or illness.

Most countries in the EU provide emergency medical attention free or at reduced rates to visitors from other member states, although immediate payment for treatment may be demanded in some countries, such as France. Travellers from EU countries can obtain a European Health Insurance Card (EHIC) in their home country, which confirms their entitlement to this scheme, although full medical travel insurance is still recommended. Following Brexit, British travellers can continue to use their EHIC card until it

expires; the UK has introduced its own version, the Global Health Insurance Card (GHIC). This card functions similarly to its predecessor, allowing British citizens access to state healthcare when visiting the EU. Some non-EU countries (e.g. Australia and Russia) offer free or reduced-rate medical care for EU members. In the USA, emergency medical treatment can be extremely expensive, and insurance premiums are correspondingly high. A list of insurers who do not load premiums against people with diabetes can be obtained from national diabetes associations.

Irrespective of medical insurance cover, it should be appreciated that emergency medical care available in some countries is suboptimal or even potentially dangerous for a diabetes-related emergency. In some parts of the world, insulin is not readily obtainable and intravenous fluids are in short supply. These considerations may influence the choice of holiday destination for people with diabetes.

Drugs and equipment

Essential items for the traveller with diabetes are listed in Table 66.6.

- *Immunization*. Routine recommendations should always be followed for the relevant destination. Occasionally, a severe reaction to a vaccine may cause a temporary rise in insulin requirements.
- *Medication*. Air travellers treated with insulin should carry an ample supply in their hand luggage. Preferably, another supply of medication should be carried by a relative or friend in case of loss or theft. When travelling by air, medication and blood monitoring equipment should not be consigned to the hold, because of the risk of losing luggage and the deleterious effects of extremely low hold temperatures on the insulin. During travel, insulin can be carried in an insulated cool bag. Treatment for hypoglycaemia should also be carried in the hand luggage; this is best in the form of dextrose tablets or sweets, as the regulations on the amount of liquid that may be carried through airport security may pose difficulties.
- *Insulin pumps*. People using insulin pumps should carry spare batteries, vials of long-acting insulin, and syringes (or pens) as a back-up in case of pump failure, and the contact details of the pump manufacturer so that a replacement can be ordered. Some insulin pump manufacturers will provide users with the temporary loan of a spare pump for a holiday. It is important that insulin pump users carry a written note of their insulin pump settings, including basal rates, bolus ratios, sensitivity factor, blood glucose targets, and active insulin time, as well as the consumable types and the pump serial number. Some insulin pumps should not be passed through X-ray security or body scanners, as these may interfere with the electronic software in the pump; pump manufacturers will provide an explanatory letter, which can be shown to security staff. Insulin pumps can pass safely through security metal detectors. The delivery of insulin from a pump may be increased if the atmospheric pressure is reduced suddenly, because bubble formation displaces insulin from the cartridge and may provoke hypoglycaemia. If cabin depressurization is severe, this could increase insulin delivery by as much as 8 units [122]. Even during normal ascent and descent, there can be slight increases and decreases, respectively, in the amount of insulin administered. Insulin pumps can also be targets for theft, as they may be mistaken for mobile phones or other electronic devices; it is important to check that travel insurance covers theft of the insulin pump.
- *Glucose and ketone monitoring*. Extremes of temperature and high altitude can disable some blood glucose meters and affect the accuracy of blood glucose test strips, although the cabin pressure of passenger aircraft (equivalent to an altitude of up to 2500 m) should not pose problems [123]. While on holiday, it is sensible to carry a spare glucose meter (and blood ketone meter if used), test strips, a replacement meter battery, and spare sensors if using CGM. If a new glucose meter is purchased overseas, it is important to remember that its default display could be in different units to the standard for an individual's home country; that is, mg/dl instead of mmol/l or vice versa. As with insulin pumps, some CGM systems should not be passed through X-ray security or body scanners, though they can be passed through metal detectors. The wireless link between CGM and the insulin pump can be an issue for some airlines; some pumps have an 'airplane' mode that can be used during take-off and landing. Current advice is that people with diabetes should discuss any medical devices that they intend to take on board an airplane with their airline.
- *Other considerations*. Those prone to motion sickness should take an anti-emetic to prevent nausea and vomiting from disrupting glucose levels. Anti-diarrhoeal agents and a broad-spectrum antibiotic should be carried, particularly if travelling to regions with a high risk of acquiring gastroenteritis. People with peripheral sensory neuropathy should take comfortable and appropriate footwear for travel and for holiday use, as foot ulceration may be caused by wearing ill-fitting sandals or walking barefoot across rocks or even hot sand.

Table 66.6 Checklist of essential items for travellers with insulin-treated diabetes.

Health checks
Diabetes annual review – if prolonged travel
Vaccinations
Visit general practitioner for prescriptions, including possible antibiotics and anti-diarrhoeal agents
Documents
Diabetes identity card/bracelet
Document stating diagnosis and treatment; letter from insulin pump company regarding X-ray machines and scanners
Copy of repeat prescription
Medical insurance and EHIC
Insulin pump company care-line number
Insulin pump settings
Equipment
Insulin vials or cartridges (also required by those on pump therapy)
Syringes and needles/pens and spare pen needles
Flask or cool bag for insulin storage
Blood glucose meter; spare meter and batteries; ketone meter (if used)
Finger pricking device and spare lancets; container for used needles
Spare glucose sensors (for continuous or flash glucose monitoring)
Spare insulin pump, batteries, and consumables
Hypoglycaemia treatment
Quick-acting carbohydrate:
Glucose drinks (screw-top container; no more than 100 ml if flying)
Glucose tablets/confectionery
Slow-acting (complex) carbohydrate:
Biscuits or cereal bars

Long flights and crossing time zones

Long flights pose several potential problems, ranging from the timing and composition of airline meals to ensuring that insulin dosages will cover the flight and adjust to local time on arrival.

Meals

Times of serving in-flight meals after take-off can usually be obtained from the airline. In-flight meals can be supplemented with a personal supply of suitable carbohydrate, but it is impractical to carry large quantities, not least because of the limits of what foods may be imported into many countries. Allowance may have to be made for delayed flights or long intervals between meals, while fatigue or travel sickness may blunt appetite.

Alcohol

Drinking alcohol before and during air travel is best avoided because of the risk of hypoglycaemia; also, the diuretic effects of alcohol favour dehydration, which has been implicated in deep venous thrombosis and pulmonary embolism during long-haul flights (although diabetes does not appear to confer greater risk) [124]. Water or non-alcoholic sugar-free drinks should be drunk liberally.

Glucose monitoring

Blood glucose levels should be monitored frequently while in transit and when changing time zones. It is often safer to allow in-flight glucose values to be slightly higher than usual to avoid the risk of hypoglycaemia.

Insulin treatment

There is no evidence-based information on how to adjust insulin dosages during flights that cross several time zones, and this probably accounts for the variability in the advice that is given [125]. Each case should be discussed individually, considering the duration of the flight and the change in time zone, the usual insulin preparations and dosages, the size and timing of meals, and the results of glucose monitoring. Some general guidelines are suggested in Table 66.7 and Figure 66.4.

Guiding principles are as follows:

- Do not aim for strict blood glucose targets while flying. A few hours of mild or moderate hyperglycaemia will do no harm and, as long as glucose levels are monitored regularly, it is safer to reduce usual insulin dose and use small additional insulin dosages rather than risk hypoglycaemia.
- Glucose levels should be checked every 2–3 hours.
- Time changes of less than 4 hours in either direction normally need no major adjustment of the usual insulin schedule: simply give

Table 66.7 Management of diabetes during long-distance air travel.

Obtain advice from the diabetes clinic before travelling
Obtain essential information, including the local time of departure, flight duration, and local time of arrival
Inform the airline that you have diabetes, especially if you are treated with insulin
Carry extra supplies of carbohydrate
Anticipate that delays may occur
Time-zone travel may necessitate two consecutive morning or evening insulin doses, before and after the flight
Ensure that you can monitor your blood glucose frequently during travel
Do not strive for meticulous control of blood glucose while travelling
Adjust insulin doses if necessary

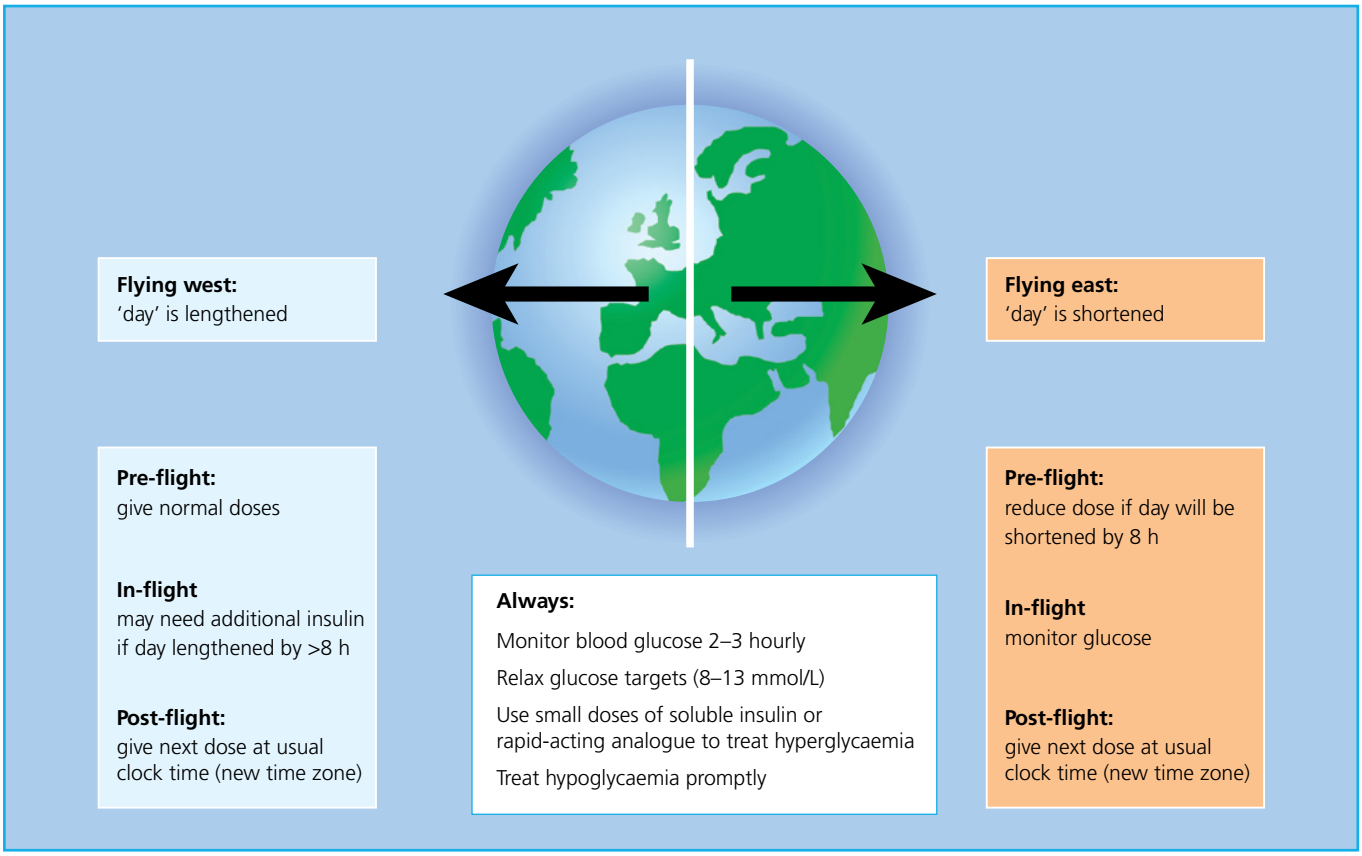

Figure 66.4 Scheme for adjusting insulin dosages during flights that cross time zones.

the next dose of insulin at its usual clock time, using the destination's time zone.

- Westward flights *lengthen* the day. Give the next dose of delayed-acting or premixed insulin at its usual clock time (using the destination's time zone). If this injection is delayed by more than 12 hours, then additional insulin with food will be needed in the interim. The most convenient way to do this is with small doses (usually a few units) of soluble insulin or a rapid-acting analogue, injected every 4 hours or so on the basis of blood glucose measurements.
- Eastward flights *shorten* the day. The next dose of delayed-acting or premixed insulin should again be given at its usual clock time (destination time zone), but because this injection will effectively be earlier than usual, the previous dose of delayed-action insulin should be reduced if the interval between the injections is less than 12 hours.
- Extremely long flights with a time shift of 12 hours or more may require two *morning* or two *evening* insulin dosages to be injected consecutively, before and after the flight.
- Any additional insulin needed to fill in long gaps between delayed-action injections or to correct hyperglycaemia is best given as small doses of soluble or a rapid-acting analogue, ideally using a pen injection device.
- Travelling across time zones is generally easier to manage when using insulin pump therapy. The *temporary basal* feature can be helpful, depending on the length of the flight and activity levels, and it is easier to administer correction boluses. It is important to adjust the clock time on the pump to the local time, to ensure that the correct basal rates of insulin are being administered [126].

Oral glucose-lowering agents

Additional doses are not usually required to cover an extended day.

Insulin treatment in hot climates

An individual's insulin requirements may change markedly in different countries, the main factors being differences in diet and daily physical activity. Subcutaneous insulin absorption can be accelerated by high ambient temperatures, such as in a sauna, and this effect has variable clinical significance in very hot climates.

Modern formulations are quite stable, but sometimes denature if exposed to high temperatures and shaken; in this case, discoloured particles or a granular appearance (distinct from the normal cloudiness of delayed-action preparations) may be seen when the insulin is resuspended. Sometimes there are no visible changes, but the insulin appears to lose its effect, with the usual dosages failing to lower blood glucose. Particularly in hot countries, insulin is best stored in a refrigerator; if one is not available, insulin can be protected by a damp flannel or a porous clay pot containing some water or wet sand, placed in a cool part of the room. Even these measures may be unnecessary, as most insulin preparations can survive being kept at 25 °C or more for up to six months and will retain most of their biological activity [127].

Food and drink

When travelling abroad, it is essential to know the basic form of carbohydrate that is eaten locally, and useful to learn to judge quantities of foods such as pasta or rice. Items selected from local menus can be supplemented with bread, biscuits, or fruit. Sugar-free drinks are difficult to obtain in many countries, but bottled water is safe and usually available.

Quick-acting carbohydrate to treat hypoglycaemia should always be carried and stored appropriately: dextrose tablets may disintegrate or set hard in hot and humid climates unless wrapped in silver foil or stored in a suitable container, while the temperature dependence of chocolate is well known. Cartons of fruit juice cannot be reused once opened; a plastic bottle with a screw top is preferable. Sealed packets of powdered glucose may be the best option for hot, damp climates.

Travelling companions should carry a supply of quick-acting carbohydrate (and glucagon) for emergency use and should know how to test the blood glucose and how to treat hypoglycaemia.

Intercurrent illness

Any intercurrent infection should be treated promptly and appropriately, with adequate replacement of fluids and carbohydrate in the form of drinks if possible. Insulin therapy must never be discontinued and dosage may have to be increased, and blood glucose should be checked every 3–4 hours, with testing for urinary ketones if possible. Usual *sick-day* rules should be followed.

Recreational activities

The impact of physical exercise and sport on diabetes is discussed in Chapter 28. People need advice about strenuous and unaccustomed exercise during holidays, such as beach sports or prolonged and vigorous dancing. Swimming alone should be avoided. The risks of alcohol and recreational drugs have been described earlier.

Leaving home

As a child with diabetes grows up, inevitably parental input to the day-to-day management of diabetes is reduced with the increasing autonomy of the adolescent. In teenage years this is often manifest by a deterioration in glycaemic levels (Chapters 69 and 70). Even in adolescence, parents or guardians still play an important role in the provision of regular meals and in the recognition and treatment of hypoglycaemia, particularly at night. Therefore, the eventual move away from the parental home can pose problems, especially if the individual with type 1 diabetes is living alone and if they move to another town. Social isolation may exist until new friends are made and access to alcohol and recreational drugs may increase, with the attendant risks that have been highlighted. Sexual activity may commence or increase, introducing issues of sexual health and pregnancy, and novel forms of exercise may be more readily available. On leaving the parental home, individuals often become removed from the familiar support of the healthcare professionals in their local diabetes centre and initially do not have the similar contact and immediate access to advice from doctors and nurses about diabetes, precisely at a time it may be most needed. It is a disturbing fact that 'living alone' was associated with a more than fourfold increased risk of mortality from acute metabolic complications of diabetes in the Diabetes UK Cohort Study [112].

Students with diabetes

Particular emphasis has been placed on the welfare of students with type 1 diabetes who have left home to attend university or college. In part, this has been because of high-profile instances where individuals with type 1 diabetes have died shortly after commencing university [128]. Several surveys have suggested that students find diabetes more difficult to manage, although this does not necessarily translate into a rise in glycated haemoglobin concentrations [129–134]. Barriers to diabetes management include fear of hypoglycaemia, diet, irregular schedules, lack of parental

involvement, limited finances, recreational drugs, and alcohol. There is a natural desire for students with diabetes not to appear different from their peers, and this may lead them to assign a lower priority to diabetes management than they would normally and to undertake potentially high-risk activities [135].

Diabetes services need to be responsive to the needs of adolescents and young adults who are leaving home. Such individuals are often poorly informed about the inherent risks associated with, for example, alcohol and drugs [108, 134] and these and other needs may not be addressed in the context of a routine diabetes consultation [133]. Before the individual leaves home, a formal re-education programme should be offered in which alcohol, drugs, exercise, sex, and sick-day management are discussed [136]. Individuals leaving home need to think about their mealtimes; it can be difficult for someone living alone to motivate themselves to prepare substantial meals and many adolescents have limited cooking skills. Regular meals are provided in university halls of residence, but the nature and content of the food, particularly the carbohydrate content, may not be ideal.

Students should be advised to monitor glucose levels frequently during examination periods. Many students report that studying and undertaking examinations can cause marked fluctuations in glucose levels; this may partly be associated with stress or varying carbohydrate intake. Both acute hypoglycaemia and hyperglycaemia impair cognitive function and can cause mood changes and may affect examination performance adversely. Therefore, students should try to optimize glucose levels during examinations and ensure that a supply of rapid-acting carbohydrate is available. People with diabetes may not recognize their condition as a 'disability', but in many countries diabetes is covered by equality or disability laws. Students with diabetes may apply for 'special arrangements' during examinations, such as taking a break if they develop high or low glucose levels, and permission to use monitoring equipment and take insulin and food/drink as required.

Many students may prefer to remain under the care of their home diabetes team, but it is important that they know how to contact local specialist diabetes services in the university town for advice or assistance. There is a real risk that students with diabetes can become 'lost to follow-up' during the transition from home to higher education. Medical practitioners in university health services have a duty to ensure that students with diabetes are offered regular diabetes follow-up. The student should be encouraged to confide at an early stage in a reliable friend or colleague about their diabetes and the potential problems that may arise [136]. Talking to recent acquaintances about having diabetes may cause embarrassment. It should be remembered that university authorities have a pastoral responsibility for students with diabetes [129].

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67 Social Determinants of Diabetes

Keri F. Kirk[1], Gerald McKinley[2], Briana Mezuk[3], and Erica Spears[4]

[1] Department of Family Medicine and Psychiatry, Georgetown University School of Medicine, MedStar-Georgetown University Hospital, Washington, DC, USA

[2] Department of Pathology and Laboratory Medicine, Schulich Interfaculty Program in Public Health, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada

[3] Center for Social Epidemiology and Population Health, University of Michigan School of Public Health, Ann Arbor, MI, USA

[4] Louisiana Public Health Institute, New Orleans, LA, USA

Key points

- Across Westernized nations, indigenous, racial, and ethnic minority populations have a disproportionate burden of type 2 diabetes.
- The conditions in which people are born, grow, work, live, and age shape the risk of type 2 diabetes, including the racial or ethnic inequities in diabetes risk, over the life course.
- These factors are collectively referred to as *social determinants of health* and describe the macro (i.e. policies and systems) and meso (i.e. neighbourhood characteristics) contexts in which individuals live.
- Meso factors that shape the risk of type 2 diabetes include local area resources and constraints (e.g. greenspace, grocery stores, safety) that shape the options individuals have for engaging in healthy behaviours that mitigate the risk of type 2 diabetes.
- Meso factors are themselves shaped by macro-level policies and regulations that affect infrastructure, zoning, workplaces, food access, and educational and economic opportunities.
- Using illustrative examples from the USA and Canada, this chapter describes how social determinants of health drive racial inequities in type 2 diabetes.
- Addressing social inequities in diabetes risk requires remedying these macro- and meso-level determinants that put minority populations 'at risk of risks'.

To accept one's past – one's history – is not the same thing as drowning in it; it is learning how to use it. An invented past can never be used; it cracks and crumbles under the pressures of life like clay in a season of drought.

James Baldwin

Diseases deemed untreatable as recently as a decade ago are now managed effectively. But each of these triumphant truths must be qualified by 'for some.' Your generation will have to deal with a growing outcome gap as some populations have ready access to increasingly effective interventions while others are left out in the cold.

Paul Farmer

Type 2 diabetes is a multifactorial disease. While the specific pathophysiological mechanisms are not fully understood, type 2 diabetes risk is influenced by both genetic liability and health behaviours. Heritability estimates for type 2 diabetes range from 20% to 80% [1], and genome-wide association studies have identified hundreds of loci [2]. Furthermore, health behaviours and their correlates (e.g. tobacco use, excess alcohol use, physical inactivity, having overweight or obesity, sleeping disturbances) are predictive of an elevated risk of type 2 diabetes. However, these individual-level genetic and behavioural factors alone do not fully explain the variation in type 2 diabetes risk. Specifically, these factors do not explain why there are substantial, and in some cases growing, disparities in type 2 diabetes risk as a function of place, race, ethnicity, and socioeconomic status [3–5]. Neither do they explain why, within Westernized, industrialized countries, marginalized groups consistently have a higher burden of type 2 diabetes despite substantial national differences in healthcare systems. Instead, research points to another set of factors, which are fundamentally social and environmental in nature, as driving these inequities.

In the past decade there has been increasing attention to the role of social determinants of health, including their role in exacerbating health inequities. The World Health Organization (WHO) defines social determinants of health as the set of conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life [6]. Social determinants of health are 'the social characteristics within which living takes place' [7]. This phrasing points to a fundamental element of the social determinants of health framework, which is that health and health behaviours are shaped by contextual factors beyond the individual; thus, population health, and health inequities, are multilevel phenomena [8]. Studies in the USA suggest that social factors are the most robust predictor of population health, even surpassing healthcare and health behaviours [9]. Environmental characteristics such as air, water, and housing quality, mobility and transportation infrastructure, availability of grocery stores and the cost of food, access to recreation facilities, and social capital and cohesion are all

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factors beyond the individual that shape health [10]. Moreover, these environmental characteristics are themselves shaped by economic policies and systems, development agendas, social norms, social policies, and political systems [10]. In sum, the social determinants of health framework reflects the complex and interdependent nature of *person* and *place* to situate *person in place*.

While social determinants of health have been examined as determinants of various aspects of diabetes care (i.e. medication taking [11], glycaemic management [12]), there also is a growing body of literature on how social determinants shape the risk of developing type 2 diabetes [13–16]. Leaders in the field have called for focused attention to understand how social determinants of health contribute to type 2 diabetes. As one example, in her 2018 address to the American Diabetes Association, Dr Felicia Hill-Briggs put forth a new initiative on establishing the scientific evidence base regarding social determinants of diabetes to inform clinical and community-based programming and priorities [17]. In 2021, this commission released its report, concluding: 'Inequities in living and working conditions and the environments in which people reside have a direct impact on biological and behavioural outcomes associated with diabetes prevention and control. Life-course exposure based on the length of time one spends living in resource-deprived environments – defined by poverty, lack of quality education, or lack of health care – significantly impacts disparities in diabetes risk, diagnosis, and outcomes' [18].

How do macro-level factors and meso-level factors shape health behaviours that influence the risk of conditions like type 2 diabetes?

As this chapter will describe how macro- and meso-level factors influence the risk of type 2 diabetes by structuring the dimensions on which individuals can make choices about health behaviours (Figure 67.1) [19, 20]. The chapter draws on Link and Phelan's *fundamental cause* [21] and Bronfenbrenner's *socioecological* [22] models, which collectively identify health as a multilevel phenomenon, shaped over the life course by factors at the macro (i.e. political), meso (i.e. neighbourhood, workplace), and micro/individual (i.e. behaviours, genetic liability) levels that intersect and interact. Beyond those proximal factors that influence the choice of specific behaviours in a specific scenario (e.g. individual preference for choosing between an apple or a cookie, etc.) [23], these multilevel factors shape *access* to grocery stores, *whether* an individual has fresh fruits available where they shop for groceries, *how much* the apple costs relative to the cookie, and so on [24]. These factors create affordances (i.e. features of neighbourhoods, workplaces, etc. that support health promotion) and constraints (i.e. barriers, challenges, and opportunity costs to health promotion) [25, 26]. By creating and reinforcing these affordances and constraints, macro- and meso-level characteristics differentiate *options* from *choices*, and then further delineate the options among which individuals can choose.

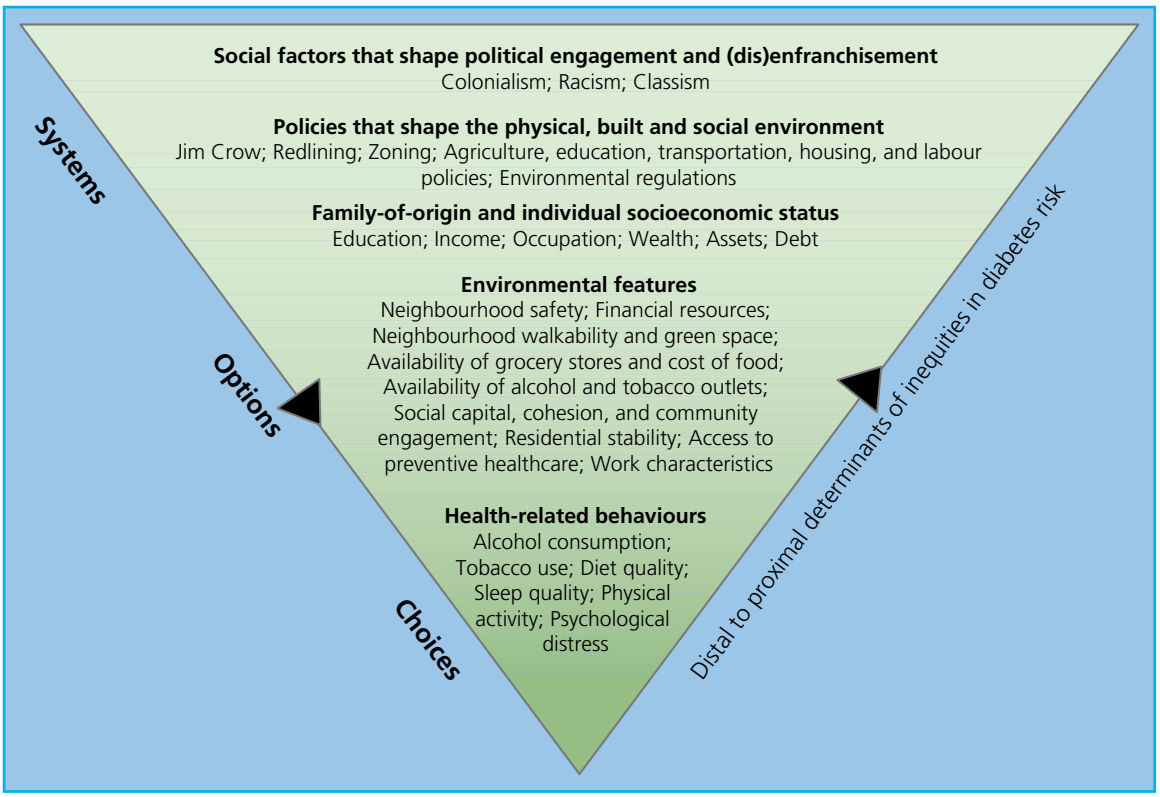

Figure 67.1 Symptoms of a system: conceptual model of how social determinants create inequities in type 2 diabetes risk. This conceptual diagram shows how pervasive systems like colonialism, historically and across generations, manifest policies that shape the options that individuals have for engaging in diabetes prevention and risk behaviours as a function of factors like place, race, and socioeconomic status. While individuals' health behaviours are the primary targets of intervention for healthcare providers, the underlying systems and options that create those differences are not; however, without addressing these underlying factors, efforts to address population inequities in diabetes risk will not be successful.

To illustrate this idea, this analysis will focus on nations that share a common history as part of the British colonial system (e.g. UK, USA, Canada, and Australia) and detail two examples from the USA and Canada to show how social determinants of health operate across geographical boundaries. The chapter concludes with key takeaway messages for clinicians and public health practitioners.

Scope of social inequities in type 2 diabetes in select former British colonies

Social inequities in type 2 diabetes exist across all dimensions of this disease, including incidence, prevalence, complications, and mortality. Figure 67.2 shows the prevalence of diagnosed diabetes from population health surveys of the UK, USA, Canada, and Australia as a function of race or ethnicity. While the plot represents cases of both type 1 diabetes and type 2 diabetes, given that these are based on general population samples the overwhelming majority of cases represented here are type 2 diabetes. This figure begs the questions: Why is it, regardless of the specific political system, healthcare system, geography, or specific ancestry, race, or ethnic group, that marginalized groups in former British colonies have a disproportionate burden of type 2 diabetes? What could explain this striking pattern that holds across these different healthcare systems?

This plot is only a snapshot of the disparities in diabetes burden. Not only is the prevalence of diabetes higher in these marginalized groups, but the age of onset is also significantly lower. Type 2 diabetes has become a disease of mid-life rather than later adulthood, particularly for racial minorities. For example, in the USA the prevalence of type 2 diabetes at age 45 years among African Americans and Latinos is twice that of non-Hispanic whites (10.9% and 9.4%, respectively, vs 5.2%), and the mean age at diagnosis of type 2 diabetes among these minority groups is eight years earlier than that of non-Hispanic whites [32]. Racial and ethnic minorities also have a greater risk of developing complications from diabetes over time, including end-stage renal disease, amputation, vision impairment, and cardiovascular disease [32, 33]. Unsurprisingly, they also have greater healthcare utilization and costs associated with type 2 diabetes [32, 34, 35]. While these examples are from the USA, similar inequities exist in Canada [36]. As a result, any effort to address the substantial financial burden of type 2 diabetes within healthcare systems [37–39] must seek to address and remedy such disparities.

Beyond their influence on the risk of type 2 diabetes, social determinants of health also have impacts on disease self-management. For example, a recent mixed-methods investigation of people with diabetes living in the UK, the USA, and Australia identified many social determinants of health as common barriers to effective self-management, including financial constraints, psychosocial distress, and competing demands (particularly related to work) [40]. These barriers are strongly correlated with socioeconomic status (i.e. income, education, wealth) [41, 42]. Clinical guidelines from organizations such as the American Diabetes Association now explicitly call on clinicians to address the social determinants of health such as health literacy and food insecurity as part of comprehensive diabetes care [43].

Colonization as a frame for examining social determinants of type 2 diabetes

As defined by the WHO, social determinants of health include social, economic, and political systems. Pursuant to this broad definition, many scholars have named ideological stances, such

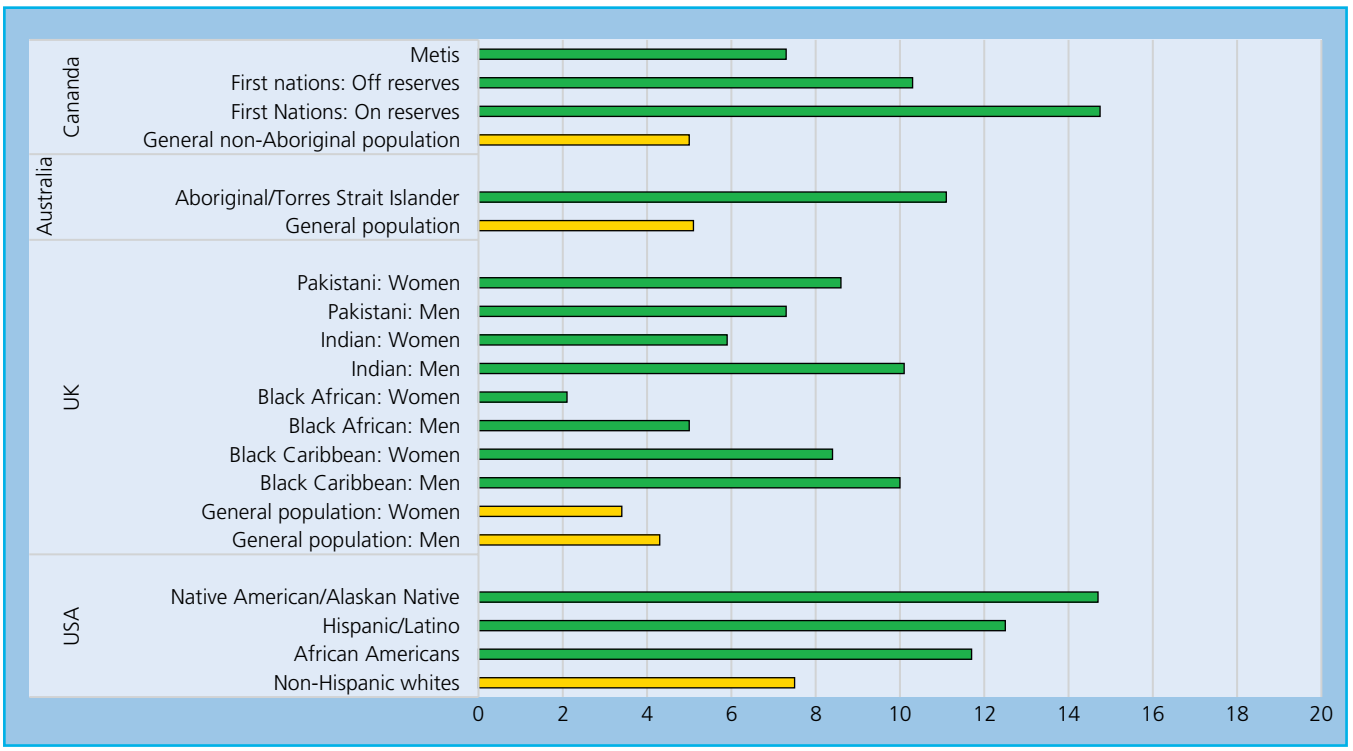

Figure 67.2 Prevalence of diagnosed diabetes by race and ethnicity in the USA, UK, Canada, and Australia. Age-adjusted prevalence of diagnosed diabetes (type 1 diabetes and type 2 diabetes) by ethnic group in select nations under the British colonial system. Source: Data for the USA from Centers for Disease Control and Prevention 2020 [27]. Data for Canada from Government of Canada 2011 [28]. Data for the UK from NHS Digital 2004 [29]. Data for Australia from Australian Bureau of Statistics 2013, 2014 [30, 31].

as racism [44], or their institutional manifestations, such as racial discrimination [45] or worker exploitation [46], as determinants of health. However, while there are exceptions, few have explicitly tied these ideas and structures to a broader historical lens, one that recognizes that while the specific terminology for these systems changes over time, they still share a common function of marginalizing particular groups from resources and status.

As the focus of this chapter is to highlight how social determinants of health shape type 2 diabetes risk in four nations that were part of the British colonial system, the term *colonialism w*ill be used as an overarching frame for understanding disparities in type 2 diabetes risk. This term is particularly appropriate, as the chapter will use case examples to illustrate how social, economic, and political systems have shaped type 2 diabetes risk in Indigenous populations (i.e. First Nations in Canada) and groups that were subject to the British slave trade (i.e. African Americans). Colonialism is a more appropriate term than related alternatives (i.e. racism, discrimination, other specific forms of bias) for two reasons. First, there is substantial geographical variability in the definition and measurement of race and ethnicity globally, and thus the applicability of those concepts may not be readily apparent to all readers. Secondly, terms like racism focus on between-group marginalization, while colonialism reflects a broader social construct that acts both across and within groups (i.e. colourism) [47, 48]. As such, limiting the discussion to more specific terms obscures the more general expression of this ideology, particularly its historical context [49].

Type 2 diabetes among First Nations communities in Canada

In this example we will refer to Indigenous peoples as the original inhabitants of what is now Canada, including First Nations, Metis, and Inuit populations. Aboriginal denotes the legal term used for Indigenous populations in the Canadian Constitution Act of 1982. First Nations, previously called 'Indians', comprise status and non-status populations. Metis are a distinct nation, who descended from First Nation and early European fur traders, and whose rights are protected under Section 35 of the Constitution Act of 1982. The Inuit are the original inhabitants of the Arctic regions of Canada, who also have their rights protected under Section 35 of the Constitution Act of 1982. Each Indigenous Nation has its own history, culture, language, and ties to its land. In this case study, we will focus on diabetes in First Nations communities in Northwestern Ontario, who are mainly made up of Anishinaabek, Oji-Cree, and Omushkego Nations. Because Canada is a part of the British Commonwealth, we will refer to the state as the Federal Crown to represent the federal government and the Provincial Crown to denote the governments of the provinces.

We explore the *fundamental causes* of type 2 diabetes in First Nations communities in Canada. Defined by medical sociologists Link and Phelan in 1995, the fundamental cause framework [21] describes how social structures put individuals *at risk of risks*, regardless of specific pathological processes, in order to explain social inequities in health more broadly. This framework posits that socioeconomic status, which shapes access (or lack thereof) to material, social, and educational resources, has direct and indirect impacts on population health [21]. It follows that health outcomes essentially pool in specific populations, because the risk factors for diseases are elevated in the socioeconomic context in which they live and limit the choices those contexts afford for responding to those risks for all individuals in the group. In addition, the outcomes tend to persist and become cumulative in the population, because macro-level factors are slower to change and have a longer-term, intergenerational impact on health [50].

In the context of type 2 diabetes in First Nations populations in Canada, this fundamental cause framework ties outcomes to the unique constitutional relationship between the Federal Crown and Indigenous peoples. It is a relationship, and the colonial history of abuse associated with it, in which the Federal Crown gave itself a fiduciary power over Indigenous populations. Herein lies the key elements that contribute to macro-level factors causing increased type 2 diabetes in the Indigenous population. There is historical and ongoing colonial oppression in which the Crown uses its power to limit the choices available to Indigenous communities and provides substandard options for the care of their health.

Burden of type 2 diabetes among First Nations communities in Canada

As shown by Figure 67.2, while the prevalence of diabetes in the general Canadian population is approximately 6%, the lifetime risk of diabetes is 8 in 10 for First Nations people [50], with women about twice as likely to be affected as men [51]. While type 2 diabetes risk increases with age, in First Nations people there has been a rapid rise in the incidence of this condition among adolescents [52]. The prevalence of diabetes in the First Nations population in Ontario has grown significantly faster than in the non-First Nations population in the province; for First Nations people, the age-adjusted prevalence increased from 11.1% in 1995 to 16.6% in 2014, compared to from just under 4% to approximately 8% during this same period for non-First Nations people [53]. Moreover, as illustrated by Figure 67.2, this increase was particularly severe for the on-reserve population, which had a point prevalence of 18.7% in 2014 [53].

History of colonization and the development of a fiduciary relationship

The fiduciary relationship between the Federal Crown and Indigenous peoples grew out of an *unequal* relationship developed under British colonial history [54]. Legal cases such as *Sheldon* v *Ramsey* (1852), where the Bench's statement that 'the Crown should be in a situation to protect their interests and treat them as people under its care, not capable of disposing of their own possessions' reflected the dominant perspective that Indigenous populations were unable to take care of themselves [54]. Constitutionally, the development of the fiduciary relationship is tied to several important legal documents originating from Great Britain and from within Canada. By exploring how the legal documents embodied colonialist ideology and removed choices available to Indigenous populations, we see their impact on the current type 2 diabetes epidemic in Canada.

The first document is the Royal Proclamation of 1763 by George III, which officially claimed territories in what is now the USA and Canada for the Crown. To guarantee access for the Crown to the wealth from the natural resources in the territory, the Crown declared that all lands not currently under British control were the property of the Indigenous peoples who reside on them and that only the Crown has the legal right to negotiate for their surrender. In doing so, the Crown established a nation-to-nation relationship between itself and the Indigenous populations, and established the need for the treaty system which is still in place in Canada. In short, the Royal Proclamation established that a treaty between the Crown and the Indigenous populations is required before title to the land can be transferred. It also establishes the dominance of British

colonial law in Canada, and helps establish a moral and legal stewardship of Indigenous peoples by the Crown in Canada [54].

The significance of the Crown–Indigenous relationship shifted during Confederation in Canada in 1867, when Section 91 [24] of The British North America Act identified 'Indians and lands reserved for Indians' as a responsibility of the Federal Crown, or Government, in Canada. The British North America Act moved the relationship from nation-to-nation to one of responsibility through Section 91 [24]. The responsibility of the Federal Crown to Aboriginal Peoples (First Nations, Inuit, and Metis populations) and the Royal Proclamation of 1763 were later enshrined in the Canadian Constitution Act of 1982. The overall result is a situation for Indigenous peoples that has been described as *Citizens plus* [55], whereby Indigenous people are part of the Canadian population, but with a unique constitutional relationship with the Crown where the Crown has a fiduciary responsibility to Indigenous people.

The interaction of law, colonialism, and control is most notable in the still-existing Indian Act, originally written in 1876, which transitioned moral understandings of stewardships into Status Indians becoming wards of the Federal Crown [56]. The Indian Act was the amalgamation of existing regulations that sought to control Indigenous populations and their lands for the benefit of the Crown. Guided by the ongoing assumption by many leaders in Canada in the late nineteenth to early twentieth centuries that Indigenous people were unable to take care of themselves, the Indian Act solidified total control over the lives of Status Indians. Among other aspects, the Indian Act decided who was a Status Indian, controlled reserve lands, limited communities' ability to practise their culture and traditions, and replaced local leadership with Crown-controlled governments or 'Indian agents'. The current iteration of the Indian Act (1985) continues to define and control Indian Band (Canada does not use the term tribe) membership lists, reserve lands, housing and property descent, wills, 'mentally incompetent Indians', guardianship of children, Band finances, loans, and education. On reserve, health falls outside of the Indian Act and the Canada Health Act, and is supported via the Health Canada First Nations and Inuit Health Branch [57].

The Indian Act, the Treaty process, and the establishment of the reserve system in much of Canada during the late nineteenth and early to mid-twentieth centuries had a significant impact on the social, political, economic, and cultural lives of First Nations peoples [58]. During this time, First Nations children living on reserve without access to a day school were required by law to attend a live-in Indian residential school, where they experienced high levels of abuse and many lost access to traditional hunting, navigation, and language skills [59]. The expansion west of the Canadian state and increased immigration significantly altered traditional food procurement and availability for First Nations peoples. As farming increased, hunting territories were decreased and traditional foods including the bison and many plants were replaced with those from Euro-Canadian farms [60]. By the mid-twentieth century, self-sufficient populations were becoming increasingly dependent on the Federal Crown and non-traditional employment for education, employment, income, and access to food [61].

The result is a context where the Federal Crown created a unique relationship with Indigenous people in Canada through the Constitution Act of 1982 and all its historical antecedents. That relationship, finally identified as a fiduciary relationship in *Guerin* v *The Queen* (1984), is mostly administered through the Indian Act, but with significant gaps in healthcare. In relation to type 2 diabetes the legal relationship becomes more problematic, because healthcare in Canada through the Canada Health Act 1985 is a responsibility of the Provincial Crown. The healthcare for First Nations people living on reserve is administered by the Federal Crown through the Health Canada First Nations and Inuit Health Branch, which is separate from the standard healthcare system that other Canadians access.

The individual behavioural risk factors for type 2 diabetes are well established and documented. In contrast, a fundamental cause approach focuses on the macro-level factors, which cause those individual risk factors to accumulate within specific populations. Policies, laws, and regulations that limit choices and provide less appropriate options make any individual's attempts to mitigate health risks, diabetes or otherwise, much more challenging.

Traditionally, First Nations communities migrated seasonally across their territories in small family units following food sources. In summer, the interconnected waterways in the regions provided the means to travel. In winter, snowshoes and dog teams aided movement. Food was unprocessed and the caloric cost of accessing it was high. Because of the remoteness of the area, many communities were relatively unaffected by colonial changes until the early twentieth century when treaties, compulsory Indian residential school attendance, and increased resource extraction brought greater changes to the area. After signing treaties communities were relocated to their allocated Reserve Lands and infrastructure, including nursing stations and housing, was provided under the direction of the Federal Crown.

History of the diabetes epidemic in Northwestern Ontario

Northwestern Ontario officially transferred to Canadian control with the signing of Treaty No. 3 in 1873, Treaty No. 5 in 1875, and Treaty No. 9 in 1905–1906 and 1929–1930. The region is still considered to be remote, with many of the northern communities being accessed only by air or waterways, with winter roads available for a short period each year. The region comprises northern boreal forest and muskeg swamp towards Hudson Bay. The medical hubs in the region include the City of Thunder Bay, located on the northwest shore of Lake Superior, and Sioux Lookout, which is in Treaty 3 territory. The Sioux Lookout Zone Hospital, a segregated hospital for Status Indians living on reserves in the area, operated until 1992 and was active in responding to the emerging diabetes epidemic.

Rare in the region prior to the changes introduced after treaties were signed, the outbreak of diabetes in First Nations communities in Northwestern Ontario began in the 1950s [62]. The increase in type 2 diabetes coincided with the rapid changes that contributed to a nutritional transition, changes to physical activity in the population, and increased stress [53, 60, 63]. Excess diabetes risk became increasingly concentrated across generations through a variety of mechanisms. For example, in 2012 Millar and Dean identified intrauterine exposure to maternal obesity as an important intergenerational risk factor for type 2 diabetes [64]. A dietary transition took place in the region as communities lost access to their traditional lands through the Indian Act's pass system [53, 60, 63]. This transition caused a sudden shift from traditional country foods (i.e. moose, deer, caribou, fish, local plants) to store-bought, shelf-stable, high-calorie, and lower nutritional density processed foods [63]. This change in diet was associated with an increasing incidence of type 2 diabetes in these communities [65]. Moreover, the high cost of these new food sources, due in part to the remoteness of the region, is associated with an increased risk of food insecurity [66], which itself is associated with the risk of type 2 diabetes [67].

Beyond food access, the built environment itself may be a contributing factor to type 2 diabetes, particularly through the ways in which poor-quality and ageing infrastructure has impacts on chronic stress. Under the Indian Act, housing on Indian reserves is provided by the Federal Crown. Individual Band members do not own their house or the land it sits on. Robert Robson noted that 'A large portion of the estimated 89,000 on-reserve houses in Canada, are in poor condition, overcrowded, unaffordable, improperly serviced, poorly sited and generally, inappropriate given the culturally based shelter needs of the approximate 423,000 on-reserve residents' [68]. Housing quality is associated with multiple aspects of health, including type 2 diabetes [69]. Many communities continue to struggle with access to safe drinking water. First Nations communities are more than 90 times more likely to lack access to clean, running water, and Ontario-based First Nations communities experienced 402 drinking water advisories between 2004 and 2013 [70]. The biological manifestations of chronic stress associated with living in a colonial system have been identified via increased levels of hair cortisol in First Nations communities in Ontario [71, 72].

These type 2 diabetes risk factors developed together with the changes experienced by the population as a result of the policy actions of the Federal Crown. Crown efforts to gain control of the natural resources in the region, and its ability to act on the Indigenous populations through the power of the Indian Act, circumscribed the local Indigenous population's abilities to make the lifestyle choices of past generations [60]. The Act also encompassed healthcare access decisions; until the Sioux Lookout First Nations Health Authority was established in 1990 [73], healthcare access was limited to the former Zone Hospital, which was controlled by the central Canadian Government and the Inuit Health Branch of Health Canada. Centralized control of the funding mechanism has often meant that financial resources are siloed and the local level has little opportunity to reallocate funding to respond to their needs and priorities [54].

Legacy of colonialism and burden of diabetes in First Nations communities

As the example of Northwestern Ontario illustrates, both historically and in the present day, the Federal Crown limits the options available at the community level that would allow First Nations individuals to make lifestyle changes often recommended to prevent or treat type 2 diabetes. Consistent with the fundamental cause framework, this example shows how macro-level political and social factors contribute to the widespread burden of type 2 diabetes and related health conditions in Indigenous populations in Canada.

Clinical treatment guidelines continue to focus on the role of individual health behaviours as primary targets for type 2 diabetes prevention and management [60]. However, if the fiduciary relationship continues to circumscribe the options that individuals and communities have available to choose from, these efforts to change health behaviours will have little impact on the epidemic. These macro policies have shaped the environmental context of Northwestern Ontario and other First Nations communities, and these contexts are generally characterized as having limited options for engaging in physical activity, for adopting a healthy diet, and for having adequate shelter and safe drinking water. These are not simply unfortunate circumstances; they are the downstream effects of a Crown–Indigenous relationship that was founded in a colonial setting.

Type 2 diabetes among African Americans in the USA

Just as the effects of colonialism have continued to influence the health of Indigenous populations, the lasting effects of colonialism on the descendants of enslaved Africans in the USA persist within present-day social inequities, including in health. Since the Emancipation Proclamation of 1863, which freed enslaved persons in the USA, the country has found ways to perpetuate separate and unequal systems of treatment for African Americans. Perhaps the clearest demonstration of this is the enactment of Jim Crow laws in 1877 (*Plessy* vs. *Ferguson*), after the US Supreme Court ruled that segregation of public spaces was permissible. State and local governments, protected by this declaration, could formally marginalize the rights and opportunities of African Americans until the signing of the Civil Rights Act in 1964.

Geographical separation and exploitation in US Housing

For the nearly 100 years where these legally sanctioned, racist practices were in place, they continued to keep African Americans on an unlevel foundation in terms of the factors that we now call social determinants of health, including built environments, labour practices, educational opportunities, policing systems, and penal guidelines. The release from this not so distant past has been slow and unsteady, with new laws upholding old standards. For example, the practice of *redlining*, which is a form of lending discrimination, was federally sanctioned by the National Housing Act of 1934 [74]. This policy allowed lenders to support the practice of racial segregation by refusing mortgages in and around African American neighbourhoods, which were demarcated on maps with a red outline, hence the term. These undesirable properties cast away by the white racial majority restricted Black housing options by limiting the choice of community. The surrounding lands of these neighbourhoods, devalued by proximity, became an option for retailers and enterprises deemed unsuitable for white neighbourhoods [75]. While these lending practices were formally disallowed by the Fair Housing Act of 1968, the practice has been woven into the fabric that is the present-day USA, as issues of neighbourhood segregation and negative health outcomes are seen in communities across the country [76–79]. Many built environment features that are tied to type 2 diabetes risk, including inequitable food security [80], alcohol outlets [81], tobacco outlets [82], and gun violence [83], are echoes of historical, racist practices of land distribution and use like redlining.

Illustrating the centrality of place to racial inequities in health, work by LaVeist and others has shown that *racial* disparities in health, including in the prevalence of type 2 diabetes, are small or non-existent when comparing white Americans and African Americans who live in the same low-income, urban environment [84–86]. These racial gaps in type 2 diabetes are not eliminated because African Americans in these low-resource settings have a lower prevalence of type 2 diabetes than those in the USA as a whole (10.4% vs 10.5%, respectively). Rather, the gaps are eliminated because white Americans in these low-resource settings have a *significantly higher* prevalence of type 2 diabetes than white Americans in the USA as a whole (10.1% vs 6.6%, respectively) [84]. The implications are twofold. First, low-resource urban settings are associated with elevated type 2 diabetes risk in a similar manner for both African Americans and white Americans; and secondly, the

findings suggest that the overall prevalence of type 2 diabetes is higher among African Americans relative to white Americans because, at least in part, they are far more likely to live in such low-resource settings [74, 75].

How political and social systems narrow options for individual choice

The practice of redlining, and the social structures that supported such acts of racism, serve to minimize options and promote suboptimal choices for African Americans. The relationship between inequitable resources and access to care has been repeatedly linked to negative health outcomes in African American communities [87–90], including the devastating effects of Covid-19 [91]. Food systems, in particular, have adverse effects on type 2 diabetes disparities [92, 93]. African Americans have higher rates of morbidity and mortality for several chronic conditions that are linked to health behaviours, including type 2 diabetes (Figure 67.2). The role of social structures in these disparities is a function of the intersection of race and place [94, 95]. African Americans are more likely to reside and work in settings characterized by an imbalanced ratio of positive to negative coping resources [80, 81, 96, 97]. These contexts cannot provide the social or material support needed to address chronic stressors (i.e. financial insecurity) and broader uncontrollability and unpredictability in daily life. These conditions are inextricably affected by social inequities in the distribution of power, wealth, and resources [18].

While it is tempting to understand the case of racial disparities in type 2 diabetes as solely a function of socioeconomic resources, empirical studies indicate otherwise. While poverty contributes and exacerbates type 2 diabetes risk among African Americans [16], better socioeconomic status does not eliminate racial disparities in type 2 diabetes or related conditions. Instead, somewhat paradoxically, other systematic inequities diminish the expected returns of gains in socioeconomic status for a range of health outcomes. For example, gains in household income translate into smaller improvements in health for African Americans compared to non-Hispanic white Americans [98]. Consistent with this notion, while higher levels of education are associated with better self-rated health for all racial and ethnic groups, these gains are smaller for African Americans compared to white Americans. The inverse association between income and poor health, particularly obesity, is generally diminished in Black Americans relative to white Americans [99]. Within the African American population, numerous studies report that socioeconomic status is positively associated with depression, a contrast with the inverse or null relationship observed in other groups; this reflects, in part, different experiences of racial discrimination, particularly in the workplace [100, 101]. Additionally, even affluent African American neighbourhoods generally fall short of residential parity when compared to white American neighbourhoods of similar socioeconomic status [102].

These diminished returns are attributed to a myriad of social, political, and economic factors associated with Black race, such as experiences of discrimination, neighbourhood segregation, depreciated value of educational attainment as it relates to employment opportunities, pay inequity, and experiences in the healthcare system [45].

Understanding within-group variability to enhance the tailoring of prevention efforts

Although many social determinants of health are correlated with Black race in the USA, the heterogeneity within the African American population is understudied [98]. For example, there is little research examining the relationship between middle-class African Americans and their type 2 diabetes knowledge, risk behaviours, and protective factors [103]. The African American middle class comprises individuals who are frequently still connected to, or recently removed from, impoverished roots [104]. Additionally, this population is not far removed from a history of segregation and discriminatory practices [84, 105–107], which has a present-day impact on learned health behaviours and the built environment it inhabits.

As another example, despite robust experimental evidence of effectiveness, standard diabetes-prevention interventions have suboptimal results among African American women [108]. These results have been attributed, broadly, to a lack of cultural relevance in these interventions [109]. Even evidence-based, largely successful programmes like the Diabetes Prevention Program (DPP) have had difficulty successfully motivating behaviour change in African American women [110]. Moreover, using the DPP's standard design, the programme has been largely unsuccessful in promoting weight loss in this group [111, 112]. Two out of every three African American women have significantly less mean weight loss than their white American counterparts while participating in DPP programmes [112]. These disappointing outcomes point to the importance of prior research describing the unique social and environmental factors that influence weight gain and/or deter weight loss in this population [113–115].

There is a need for additional efficacy trials of the DPP that acknowledge the unique context of African American women living in urban environments to ensure reliability and effectiveness in this high-risk population. Unfortunately, there are critical gaps in the literature responding to how these factors perpetuate type 2 diabetes disparities in African American women. This group experiences intersecting social stressors related to their race and gender that influence health behaviour outcomes. The outside forces and lost locus of control associated with systemic social stressors (e.g. racism, sexism) are qualitatively unique in their effects on the body. Additionally, inequalities (e.g. food quality, green spaces) in the built environments where African American women work and live also influence options and choices around health behaviour maintenance. Successful intervention design for racial minority communities must consider how these unique stressors influence health behaviours. DPP adaptations have been more effective with African American women when specifically tailored for this population [114–116]. These adaptations, however, are limited in number and setting variability.

Relationship between social determinants of health and diabetes healthcare

Best-practice guidance on addressing the social determinants of diabetes care has been presented in a rather straightforward manner [43]. However, the challenge for healthcare providers is more complex. Is it more important to examine the options available to individuals with diabetes in order to make more actionable recommendations, which will take more time than most busy clinicians have? Or is it more important to treat the issue presenting in the clinic room, which will foreshorten an exploration of social determinants? The answer is often a difficult one given that the former typically requires collaborative care that involves stakeholders outside the healthcare system (e.g. governmental social services, community health workers, community-based organizations, mental health professionals) and critical components of such collaborative care are not reimbursable by some insurances [117]. Despite ongoing challenges

regarding the implementation of collaborative care in some medical systems, evidence shows that this model can be a valuable asset in addressing the social determinants of health, including in addressing the quality of individuals' options and choices with regard to diabetes management [18].

The choices providers make when treating people who have significant challenges in the complex web of social determinants undoubtedly have impacts on the options those individuals have for self-management of conditions like type 2 diabetes. Providers could be missing valuable opportunities to explore treatment options that would enable more personalized choices for individuals with type 2 diabetes [117–119]. For example, obesity and inactivity are common targets of diabetes care [120]. Several environmental factors intersect with established solutions for addressing obesity and physical inactivity, including the walkability of a person's neighbourhood, access to quality food options in sustainable quantities, decreased housing instability, and education beyond a high school diploma that assists with generating income above the national poverty line [12, 67, 120–122].

Unfortunately, while healthcare systems are increasingly assessing and quantifying the social environments of the individuals they serve with a given disease, the burden of addressing these contextual barriers as they relate to health and diabetes care remains on the shoulders of the individual with diabetes [123]. There are other approaches that could be taken. For example, while they are an ongoing topic of scientific debate [124], there is suggestive evidence that interventions that address food environments and improve infrastructure for physical activity can influence these types of risk behaviours [125]. Addressing the quality of food sold in neighbourhoods and infrastructure that enables physical activity would be meso-level interventions that could substantively improve the options for people that enable healthier, sustained choices.

The complex, systemic barriers to type 2 diabetes treatment warrant revisiting collaborative care as a potential solution for improved diabetes care. As an example, consider the integration of community health workers into a diabetes treatment team. Their inclusion improves diabetes self-management and overall quality of life, and reduces emergency room usage and visit attendance [126–128]. In most cases, community health workers also have many social determinants of health in common with their patients with a given disease (e.g. racial or economic background, cultural norms), which enables trust building and rapport outside of visits with other medical or non-medical providers [127, 129]. A growing body of research [130] has demonstrated that the integration of community health workers into healthcare teams improves diabetes outcomes [127]. This provision of collaborative care with a person-centred approach increases the likelihood that the individual needs, preferences, and values of a person with diabetes are met within a larger systemic context [131].

Conclusion

As part of its 2017 report *Health in All Policies* [132], the WHO stated: 'Health is a political choice. Political decisions can impact on economic and social inequities, including through policies which shape unhealthy living and working environments, or which fail to address inequities of gender, race, and ethnicity.' Social determinants of health are not simply unfortunate circumstances that make it difficult to prevent or manage type 2 diabetes. Rather, they are systematic and reinforcing structures that have long-standing, intergenerational impacts on type 2 diabetes risk. We observe that obesity, diabetes, and hypertension are more common and more severe among First Nations or African Americans, but that observation is simply a symptom of these systemic factors that drive racial inequities, including in health.

Although clinical trials such as the DPP [133, 134] and similar efforts have demonstrated that lifestyle interventions can reduce the incidence of type 2 diabetes among individuals at high risk, effectively translating such multicomponent, sustained programmes into areas and communities disproportionately affected by type 2 diabetes remains a major challenge for public health [135, 136]. Social determinants of health are an important component of this translation gap. Efforts to tailor the DPP and similar health behaviour programmes will likely continue to have only modest effectiveness, because these tailoring efforts often only affect the choices individuals make (e.g. choosing a healthy option for a meal), not the options they have to choose from (e.g. the availability of affordable, healthy food in their local grocery store) [15, 16, 97, 137, 138].

Social determinants of health systematically shape the *options* individuals have for engaging in type 2 diabetes prevention behaviours, and therefore have direct impacts on the *choices* that individuals make. In Figure 67.3, we revisit and adapt Bronfenbrenner's model to incorporate system-level considerations from the case examples laid out in this text, highlight potential consequences, and then sample considerations that healthcare systems and/or providers can implement to improve the individual's options and subsequent choices related to type 2 diabetes care [139].

Reconsidering the role of individual-level factors in the type 2 diabetes epidemic

Recall that this chapter began with the statement that type 2 diabetes is a multifactorial disease. We close with a thought experiment drawing on Rose's seminal work 'Sick individuals, sick populations' [140]. Imagine two nations. Nation A has a policy that every adult must smoke two packs of cigarettes a day, which is enforced with 100% fidelity; Nation B has access to tobacco but no such policy, and there only 20% of adults smoke. What will be true about the incidence of diseases like lung cancer, which are strongly associated with tobacco use but have a multifactorial aetiology [141], when comparing these two nations? Clearly, the rates of lung cancer will be much higher in Nation A compared to Nation B. What will be true about the association between tobacco use and risk of cancer in Nation A? Because 100% of the population smokes, there is no individual variation in the exposure, and thus there will be no relationship between tobacco use and likelihood of cancer in Nation A. Instead, as this is a multifactorial disease, the primary factors that influence risk of lung cancer in Nation A will be those that *do vary* between individuals, including genetic liability. In contrast, because there is individual variation in smoking in Nation B, tobacco use will substantially influence risk of disease in this context. Even though a macro-level factor (e.g. a policy that mandates tobacco use) is the reason Nation A has higher rates of lung cancer than Nation B, it will be an individual-level factor (e.g. genetics) that explains why any one individual in Nation A becomes sick. Nation A will see lung cancer as a disease driven by genetic liability; Nation B will see lung cancer as a disease driven by behaviour. They will both be correct, from their perspective. But the following is also true: the fundamental reason why there are more sick individuals in Nation A compared to Nation B is because of policy.

The parallel to type 2 diabetes is as follows. Historically and continuing to the present day, racial and ethnic minority groups have

Systemic level	SDOH	Individual result	Impact on options	Example action	Impact on choices
Macro	Colonial oppression	Chronic stress	Disparities in healthcare access for communities of colour	Increased healthcare funding to traditionally underserved communities	More equitable options for care
Macro	Systemic racism	Cardiovascular weathering	Limitation of options for residence, healthcare options, and provision of recommendations	Challenge inherent systems to ensure that SDOH that are made worse by race/ethnicity are addressed from the top down	Increased number of providers that can make appropriate recommendations for diabetes and comorbidities
Macro	Socioeconomic status	Restricted access and ability to pay for DPPs	Lack of exposure to evidence-based treatment	Improve accessibility of health promotion mediums (mobile treatment units, satellite clinics in relevant neighbourhoods)	Improved access to universal standards of care
Meso	Neighbourhood walkability and safety	Lack of inherent physical activity, potential safety concerns	Removal of options for active physical activity, income generation within neighbourhood	Collaborate with patient on determining feasible recommendations that support other areas of diabetes management and/or passive physical activity	Increased number of choices within accessible environment
Meso	Food insecurity	Dependence on cheaper, processed foods	Limits healthy food options in neighbourhoods	Partner with farmer's markets to generate reoccurring food delivery programmes for diabetes patients	Increased availability of fresh foods, whole foods, and non-processed foods.
Meso	Lack of grocery store access	Food deserts or swamps	Food insecurity	Food delivery/gift cards/vouchers from grocery stores that deliver	Allows patients to choose from healthier options
Micro	Lack of adherence or access to health behaviours promotion (physical activity, nutrition)	Elevated HbA1c, blood pressure, and other comorbidities	Restricted to medication as first line of treatment, which introduces medication adherence as another potentially difficult health behaviour to adhere to	Community-based participatory-based health behaviour interventions	Allows health systems and communities to collaborate and simultaneously support relevant choices that fit within system restraints
Micro	Genetic predisposition in systemically strained environment	Generational comorbidities	Limited options for parents limits options for children, perpetuates cycle of access issues	Ensure access to health behaviour coaching, family psychotherapy, and family education	New ideas for health promotion strategies, improved perception and navigation of barriers
Micro	Obesity	Increased risk of comorbid diagnoses	Tiered approach to care which may limit what patient can feasibly adhere to	Implementation of collaborative or stepped care model	Increases access to weight maintenance care points within current care

Figure 67.3 Links and applications between macro, meso, and micro levels as they relate to the development and management of type 2 diabetes. DPP, Diabetes Prevention Program; HbA_{1c}, glycated haemoglobin; SDOH, social determinants of health.

been subjected to policies and systems that have limited their resources and associated options for engaging in diabetes-preventive behaviours. Simultaneously, these groups have been exposed to readily available and accessible options for engaging in diabetes risk behaviours. Because of the reserve system and residential segregation, Indigenous people and African Americans, on average, live and work in environmental and social contexts that majority white American populations rarely encounter [142]. These contextual factors shape the risk of type 2 diabetes.

While colonialism is a historical idea, its relevance to social inequities in type 2 diabetes is observed today because of the correlation between race and the concentration of (dis)advantage across generations. While the biological mechanisms explaining these persistent effects are continuing to be identified [143–145], including ideas related to epigenetics and the *thrifty genotype* [146, 147], as the previous thought experiment illustrates the salience of any risk factor for a multifactorial disease is a function of the other risk factors in place. The relative availability of individual-level risk and protective factors is shaped by social determinants of health, and addressing the latter has more potential to shift population health as a whole, and to address health inequities, than addressing individual behaviour change [6, 18, 148].

Postscript

Just as we have intentionally used the term colonialism in this chapter, we have also intentionally used the term *health inequities*. It is critically important to recognize that *not all group differences in health are inequities*. The US Government defines health disparities as a particular type of health differences that are 'closely linked with economic, social or environmental disadvantage' [118, 149]. Braveman extends this to say that 'health equity is the principle underlying a commitment to reduce – and, ultimately, eliminate – disparities in health and in its determinants, including social determinants' [149]. Therefore, our choice of describing the type 2 diabetes epidemic in First Nations and African Americans as stemming from *inequities* illustrates our commitment to this principle.

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11 Diabetes in Special Groups

68 Ethnic, Cultural, and Religious Aspects to the Management of Diabetes

Wasim Hanif[1], Sarah N. Ali[2], and Vinod Patel[3,4]

[1] University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[2] Department of Diabetes and Endocrinology, Royal Free London NHS Foundation Trust, London, UK
[3] Warwick Medical School, University of Warwick, Coventry, UK
[4] Acute Medicine, Medical Obstetrics, Diabetes and Endocrinology Centre, George Eliot Hospital NHS Trust, Nuneaton, UK

Key points

- People from ethnic minority groups, such as those of Black and South Asian ethnicity, are at higher risk of chronic diseases, including type 2 diabetes.
- Compared to white Europeans, South Asian people with type 2 diabetes are also at greater risk of developing diabetes-related complications.
- Furthermore, ethnic minority populations are subject to health inequalities.
- It is important to distinguish between ethnicity and race, as they are separate entities. Race refers to the biological make-up of a person, whereas ethnicity encompasses a complex interaction of factors including cultural and religious behaviours, which can have additional impacts on health and illness.
- To understand the impact of ethnicity on diabetes, its management, and health inequalities, one must consider cultural factors including patterns of migration, diet and lifestyle, socioeconomic status, religious beliefs, language barriers, access to health services, and attitudes to medical treatment.
- This chapter explores the ethnic, cultural, and religious aspects to the management of diabetes, with the aim of improving cultural sensitivity and cultural competence.
- Greater cultural competence will allow for healthcare systems that provide care to people with diverse values, beliefs, and behaviours, with the aim of reducing health inequalities.
- Specific cultural considerations when thinking about the management of diabetes include dietary habits, physical activity, structured education, fasting, and pilgrimage.
- Ethnic minority groups remain under-represented in research studies, which hinders the development of tailored guidelines for these populations. It is of the utmost importance that the barriers to participation and retention of ethnic minority populations in research are addressed.

Recent global political and medical events have reignited discussions about race, ethnicity, and socioeconomic and health disparities; once again, the correct terminology with which to address ethnic minority groups has been challenged and scrutinized. Even before the disproportionate impact of Covid-19 on ethnic minority groups, we appreciated that people of Black and South Asian ethnicity are at higher risk of chronic diseases such as type 2 diabetes and cardiovascular disease compared to white Europeans. If we are to attempt to reduce health inequalities, including for people with diabetes, it is essential that we begin by considering the differences between race, ethnicity, and religion, and understand their relevance for health.

In this chapter we will discuss the definitions of race and ethnicity, and how ethnicity is relevant to diabetes. We consider in particular the impact of South Asian ethnicity on diabetes, as this has been documented most extensively of the ethnic minority groups; however, the general principles apply to other ethnic minority groups too.

Defining race, ethnicity, and religion

Race, ethnicity, and even religion may be of significance to the health of the person with diabetes and their diabetes management; however, the impact of this will only be appreciated if the healthcare professional and healthcare systems have an awareness of the specific definitions of race, ethnicity, and religion and the influence they have on one's life and health beliefs. Race, ethnicity, and religion are distinct from one another and each individually may have a bearing on a person's diabetes management and care.

Race is often used interchangeably with ethnicity; however, they have different nuances [1, 2].

Race refers to the biological make-up of a distinct population distinguishable from others by genetic or morphological characteristic differences [1–5]. By this definition, the world population can be divided into four major races: African (Black African), Caucasian (White, Middle Eastern, South Asian), Mongoloid (Sino-Asian

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including Chinese, Japanese, Korean, Native American), and Australoid (Dravidian, Australian Aboriginal) [6].

Ethnicity, however, refers to the grouping of people by shared cultural characteristics influenced by heritage, language, history, religion, nationality, customs, and geographical and ancestral origins [1, 2].

Religion refers to the belief and worship of a sacred power, usually a deity (deities) [7]. The major recognized religions (ordered based on the approximate number of adherents) are Christianity (2.2 billion), Islam (1.6 billion), Hinduism (1.0 billion), Buddhism (490 million), Shintoism (104 million), Sikhism (30 million), Judaism (14 million), and Taoism (12 million). Other important religions include Confucianism, the Baha'i faith, Jainism, and Zoroastrianism. The numbers of atheists (and those who are secular, non-religious, or agnostic) is 1.13 billion [8, 9].

Khunti et al. make the cogent point, especially in the time of the Covid-19 pandemic, that using the definition of race to address inequalities is flawed, as it indiscriminately combines people from different geographical, behavioural, social, and cultural backgrounds, as well as focuses on skin colour [10]. The redundancy of using race is apparent from the fact that in the UK the morbidity and mortality attached to Covid-19 were greater in the Black Caribbean population than the Black African population. Defining people by skin colour does not allow for an appreciation of this heterogenicity and the cultural, social, and religious nuances that define ethnicity [11].

As such, the UK Office of National Statistics (ONS) categories, while still limited, are a good start to defining the population in groups [12]. The five ethnic groups are summarized in Table 68.1.

The UK South Asian Health Foundation (SAHF) released a statement defining ethnicity or culture as a complex interaction of a multitude of factors, giving people an ethnic belonging, which subsequently has an impact on lifestyle, health beliefs, and attitudes to illness, especially long-term conditions [13]. To understand the impact of ethnicity on diabetes and its management, one must look at these cultural factors, including patterns of migration, diet, physical activity, tobacco use, socioeconomic status, religious beliefs, language barriers, access to health services, and attitudes to medical treatment.

Table 68.1 Defining the population by five ethnic groups (Office for National Statistics categories).

White	English/Welsh/Scottish/Northern Irish/British
	Irish
	Gypsy or Irish Traveller
	Any other white background
Mixed or multiple ethnic groups	White and Black Caribbean
	White and Black African
	White and Asian
	Any other mixed/multiple ethnic background
Asian or Asian British	Indian
	Pakistani
	Bangladeshi
	Chinese
	Any other Asian background
Black, African, Caribbean, or Black British	African
	Caribbean
	Any other Black/African/Caribbean background
Other ethnic group	Arab
	Any other ethnic group

Source: Based on Office for National Statistics (n.d.) [12].

Epidemiology

The International Diabetes Federation (IDF) has published high-quality epidemiological data on diabetes collated from national and international databases. The figures are alarming, in 2021, it was estimated that 537 million people had diabetes, and this number is projected to reach 643 million by 2030, and 783 million by 2045. If diabetes was a country, it would be the third most populous, more than the USA with a population of 331 million, with only China and India having a larger population [14]. Currently, 1 in 8 adults in North America and the Middle East and North Africa has diabetes, but this figure is only 1 in 25 in Africa (Figure 68.1). An increase is predicted in all seven IDF regions [14].

From the epidemiology, we can appreciate that people with diabetes will have originated from different prevalence regions. This is significant for migrant ethnic minority groups; in addition to carrying the risk of their country of origin, migrants will also share the risk factors associated with the new environment to which they have migrated. The England and Wales Census data in 2021 recorded that 81.7% of the population were white British, Asian (Pakistani, Indian, Bangladeshi, other Asian British, Asian Welsh) groups constituted 9.3% of the population, Black groups 4.0%, Chinese groups 0.7%, Mixed groups 2.9%, Arab groups 0.6%, and other groups 1.6% [15].

South Asian diaspora

The South Asian diaspora constitutes nearly 1.6 billion people and is considerably heterogeneous, with distinct communities from Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka [13]. Thinking specifically of the UK, the very first South Asian migrants to the UK were probably the lascars (sailors and militiamen) of the East India Company, which began trading with India in 1608. However, for over 150 years significantly larger South Asian migrant communities have been present [16]. The ONS (2020) estimates that approximately 1.7 million people born in the main South Asian countries were then resident in the UK. However, the 2011 Census data identified those of South Asian ethnicity as a much higher proportion of the UK population (Table 68.2) [17].

Religion

Globally, the fastest-growing religion at present is Islam. From the 2015 data to projections to 2060, it is estimated that the global Christian population will change very little from 31.2% to 31.8%; however, the Muslim population will grow from 24.1% to 31.1%, with the Hindu population remaining stable (15.1% to 14.5%). A

Table 68.2 The South Asian diaspora in the UK.

Country of origin	UK Office for National Statistics (2020)	Census data (2011) Numbers (% of UK population)
Bangladesh	244 000	451 529 (0.7%)
India	792 000	1 451 862 (2.3%)
Nepal	66 000	
Pakistan	519 000	1 174 983 (1.9%)
Sri Lanka	103 000	

Source: Data from Office for National Statistics n.d. and 2020 [15, 17].

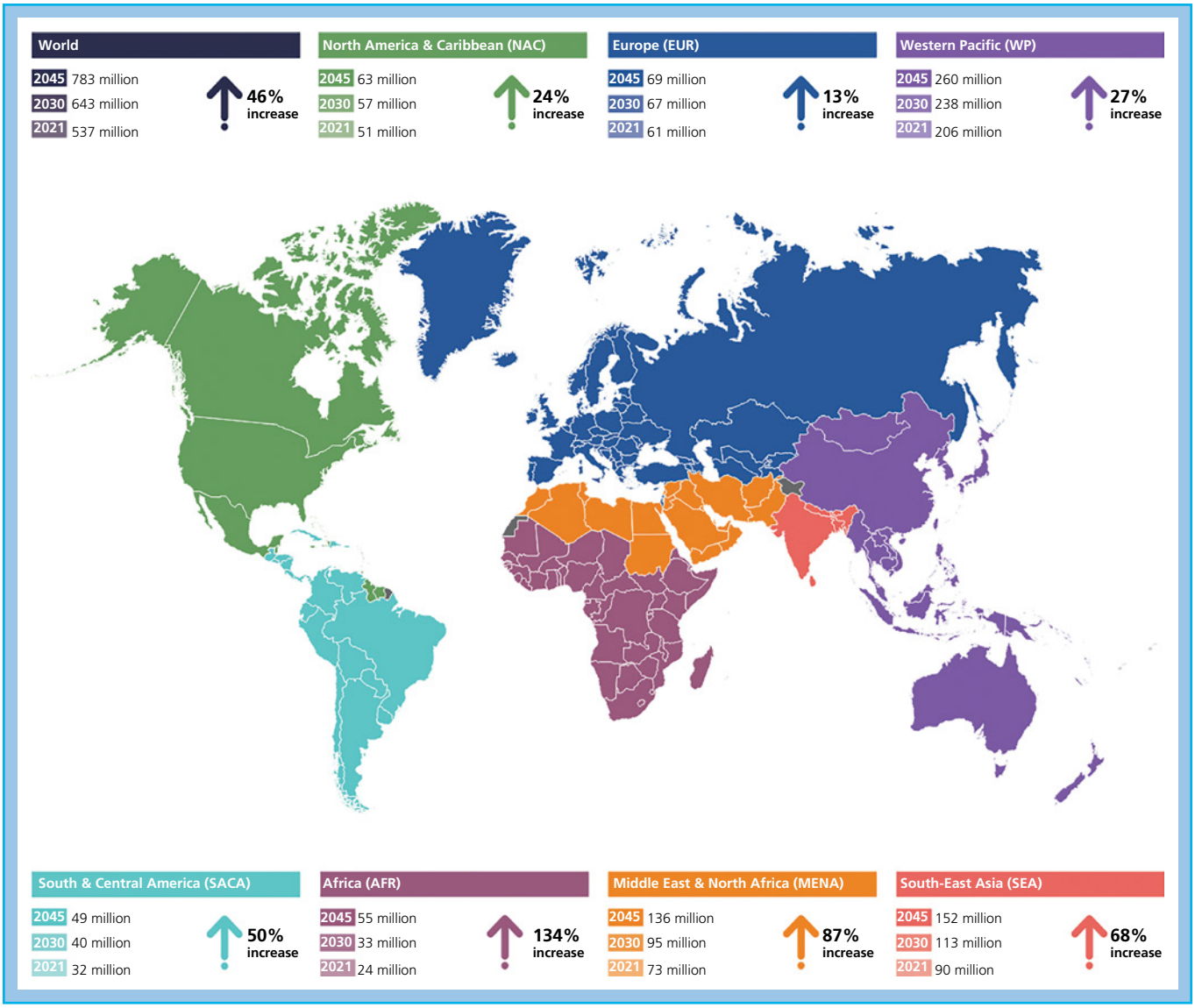

Figure 68.1 Prevalence of diabetes in different world regions with predicted increases in the next 25 years. Prevalence of diabetes in different world regions with predicted increases in the next 25 years. Source: Reproduced by permission from International Diabetes Foundation 2021 [14].

significant decrease in the Buddhist population from 6.9% to 4.5% is estimated. The Muslim population is expected to grow twice as fast as the overall global population in absolute number in all regions of the world between 2010 and 2050. Worldwide, its number is projected to increase rapidly in the upcoming decades, rising from nearly 1.6 billion in 2010 to approximately 2.8 billion in 2050 [18, 19]. Of the population of England and Wales, 46.2% identified as Christian in the 2021 Census (Table 68.3). The second largest religious group was Muslims, 6.5% of the population [15].

Table 68.3 Population breakdown by religion in the UK.

Religion (2021 census)	Number (million)	% of population
Christian	27.5	46.2
No religion	22.2	37.2
Muslim	3.9	6.5
Hindu	1.0	1.7
Sikh	0.52	0.9
Jewish	0.27	0.5
Buddhist	0.27	0.5
Other	0.35	0.6
Not stated	3.6	6.0

Source: Data from Office for National Statistics [15]. https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/religion/bulletins/religionenglandandwales/census2021. Accessed 25 July 2023.

Diabetes

Approximately 537 million people were living with diabetes worldwide in 2021, and this number will rise to 643 million by 2030, and 783 million by 2045 [14]. In the UK, 4.8 million people live with diabetes and this is anticipated to rise to 5.5 million people by 2030 [20]. The Asia-Pacific region will see the greatest numerical increase in people with diabetes. The prevalence of diabetes in the

adult Arab population rose from 2.4% to 25.4% between 1982 and 2015. By 2035, the number of people with diabetes in the Middle Eastern region is projected to rise by 96.2% [21].

People of Black and South Asian ethnicity are at a higher risk of developing type 2 diabetes compared to white Europeans [22]. The CArdiovascular disease research using LInked Bespoke studies and Electronic health Records (CALIBER) programme reviewed extracted data from 1.9 million individuals and showed that people with type 2 diabetes were twice as likely to be of either Black or South Asian origin compared to those without diabetes [23]. Furthermore, a higher prevalence of diabetes was revealed in the UK-based NHS Health Check Programme among South Asian men (9.0% vs 3.9%; p = 0.001) and women (7.4% vs 3.3%; p = 0.001) compared to their white European counterparts [24]. A more recent large-cohort population-based study confirmed that people within the South Asian community were at higher risk of developing type 2 diabetes and that those in the Bangladeshi community were at greatest risk [25].

It is important to appreciate that within ethnic categories, there is significant heterogeneity that has impacts on health risk. A meta-analysis exemplifies this point: within the European South Asian community there are differences in the risk of type 2 diabetes; Bangladeshis have the highest odds ratio (OR) for type 2 diabetes (6.2; 95% confidence interval [CI] 3.9 to 9.8), followed by Pakistanis (OR 5.4; 95% CI 3.2 to 9.3) and Indians (OR 4.1; 95% CI 3.0 to 5.7), compared to white Europeans [26].

Type 2 diabetes in ethnic minority groups appears to develop at a younger age, with a greater risk of early onset (age <40 years) in South Asians compared to white Europeans. Scottish data showed that type 2 diabetes was up to six times more common in South Asians, particularly from the age of 25 years, rather than at 40 years as seen in white Europeans [27].

Another concern in ethnic minority groups is both the late diagnosis of diabetes as well as higher glycated haemoglobin (HbA_{1c}). South Asians are more likely to have undiagnosed diabetes, and among people with known diabetes, Pakistanis, Indians, and Bangladeshis more commonly exhibited higher glycaemic levels [28].

This increased risk of type 2 diabetes in ethnic minority communities is significant, as religious and other ethnic cultural practices, such as fasting and pilgrimages, can also affect diabetes management, as discussed later.

Diabetes-related outcomes in South Asian people

Overall compared to white Europeans, South Asian people with type 2 diabetes are at greater risk of developing complications, for several reasons that include genetic predisposition, early onset of diabetes, delayed diagnosis, higher glucose levels, and a higher likelihood of treatment omission or inadequate dosing [29].

Macrovascular complications

The UK Asian Diabetes Study (UKADS) has shown that South Asians have an increased risk of cardiovascular events compared to white Europeans (adjusted OR 1.4; 95% CI 0.9 to 2.2), confirmed in other studies looking at coronary artery disease in South Asians with diabetes [30–32]. Furthermore, Scottish data demonstrated that Pakistani ethnicity was an independent risk factor for cardiovascular disease in those with type 2 diabetes (hazard ratio [HR] 1.45; 95% CI 1.14 to 1.85; p = 0.002) [33].

The West Birmingham Stroke Project findings in South Asian people with ischaemic stroke suggest that diabetes is an independent predictor of five-year mortality (OR 1.65; p = 0.039) [34]. A higher incidence of stroke was also recorded in South Asians with diabetes in the Southall and Brent Revisited (SABRE) study (HR 1.97; p = 0.038) compared with white Europeans [35].

However, utilization of culturally appropriate prevention and management strategies over the last two decades has led to an appreciable and significant reduction in the cardiovascular mortality risk in migrant South Asians [29].

Microvascular complications

There are also differences in microvascular complications between South Asians and white Europeans. Diabetic nephropathy is more common in South Asians: a meta-analysis showed a pooled prevalence ratio of 1.14 (95% CI 0.99 to 1.32; p = 0.065) for microalbuminuria in South Asians compared to white Europeans, and 1.08 (95% CI 0.93 to 1.24; p = 0.327) compared to African Caribbean people. Furthermore, chronic kidney disease progression was higher in South Asians compared to white Europeans [36].

Sight-threatening diabetic retinopathy is more prevalent in the South Asian community, but is also more likely to occur at a younger age compared to their white European counterparts [29].

In order to reduce the higher incidence of micro- and macrovascular risk in ethnic minority groups, several initiatives are needed, including earlier diagnosis of diabetes, more aggressive and sustained management of glycaemia, earlier more aggressive blood pressure management, tailored guidelines for management, as well as improved recruitment and retention of ethnic minority people in medical research.

Cultural sensitivity and cultural competence

Spirituality, personal beliefs, and religiosity can affect individuals' health and treatment behaviours positively or negatively. There are several sociocultural and religious issues specific to South Asian communities that focus on the need for individualization of care for people with diabetes.

Cultural sensitivity is the awareness and acceptance that different cultures exist; however, having this cultural knowledge is not enough on its own, as cultural sensitivity in healthcare can be construed as being patronizing and not accommodating. To improve healthcare outcomes for culturally different groups, healthcare systems and professionals need to go one step further and become *culturally competent*. This is defined as 'the ability of systems to provide care to persons with diverse values, beliefs, and behaviours including tailoring delivery to meet individuals' social, cultural and linguistic needs' (Table 68.4) [37].

Table 68.4 The difference between cultural sensitivity and cultural competence, and its impact on healthcare systems.

Cultural sensitivity	Cultural competence
Passive	Active
Patronizing	Understanding
Accommodating	Challenging
Behavioural reinforcing	Behavioural changing
No training	Requires training and knowledge

Cultural competence is a broad principle that allows us to encompass ethnicity, religion, and culture in optimizing diabetes care. It is about respecting and appreciating the cultural contexts of the life of the individual, family, carers, and community, creating an understanding about the way we deliver healthcare and then responding to the needs of our diverse population by changing practices and creating individualized or tailored pathways and guidelines for those communities [29, 37].

Cultural competence is a key aspect of providing both high-quality and safe care. If clinical care is commissioned but not accessed by the community, then an issue related to cultural competence may be present. We should ask ourselves, 'Why does one community receive and accept care while another did not?' Making effective and evidence-based care accessible will also serve to reduce health inequalities and improve outcomes in diabetes care [29, 37].

Taboos and barriers

One challenge of managing ethnically diverse communities is addressing the taboos and barriers that impede the delivery of equitable healthcare (Table 68.5). Some of these barriers are based on the communities' previous experiences, which can be described as *legacy memory*, whether that be in their country of origin or as a result of migration to the new country of residence. Another concept, fatalism, is often used as an adaptive coping mechanism for several South Asian communities. This can be expressed as *karma* or *the will of Allah (God)*. While on the surface of it fatalism appears to be a religious construct, it is not. Fatalism is a coping mechanism for death, which was a part of these communities in the developing world when there was an inability to change outcomes with interventions. The best way to address fatalism is through empowerment, by giving people the necessary knowledge such that their course of action (be it lifestyle or medication taking) can change the outcomes.

Similarly, there are other taboos, such as the restrictive use of animal-derived or alcohol-based ingredients in medicinal products or restrictions due to religious practices, including fasting, which can affect disease management. These religious and cultural beliefs should be respected, discussed, and alternative options provided where possible.

Several taboos are based on mis- and disinformation, often spread by hearsay or unregulated dissemination via social media. Despite the challenge, the disinformation must be counteracted and corrected by authoritative sources.

Table 68.5 Barriers to healthcare for ethnic minority communities.

Perception of risk
Fatalism – 'karma' or 'will of Allah'
Low confidence in the healthcare system
Distrust in healthcare professionals/healthcare system
Access barriers including language and literacy
Inconvenience
Sociodemographic context
Religious and cultural restrictions with diet, e.g. animal/alcohol-based products in medicine, fasting
Lack of communication and lack of endorsement from trusted providers and community leaders – 'familiar faces' of the community with whom people can relate
Unregulated media relaying dis- and misinformation: Indian subcontinent has some of the highest users of social media–based messaging services

Overcoming most taboos and barriers is possible by providing correct information from culturally competent healthcare professionals, in multilingual, non-stigmatizing communication in different formats (including videos, infographics, as well as written information), and with the use of community and faith champions (faces with whom people from the community can identify).

The recent Covid-19 vaccination programme initiative by NHS England, SAHF, and other organizations is a good case study where low vaccination uptake in the ethnic minority communities was turned around through positive messaging and correct information [38, 39].

The impact of ethnicity and health inequalities

Health inequalities are differences in the status of people's health, the healthcare that people receive, and the opportunities they have to lead healthy lives [40, 41]. Health inequalities can therefore cause differences in health status (e.g. life expectancy, prevalence of medical conditions), access to healthcare and treatment, the quality and experience of care (e.g. as measured by patient-reported outcome), behavioural risks to health (e.g. cervical cancer screening, smoking rates), and wider determinants of health (e.g. quality of housing) [41].

Differences in health status that lead to health inequalities can be grossly determined by four factors: socioeconomic factors (including income), geography (region as well as urban or rural), specific characteristics including those protected in law (e.g. gender, disability, and ethnicity), and socially excluded groups (e.g. people experiencing homelessness) [40]. People who experience different combinations of these factors will have varying implications for health inequalities depending on how the factors interact.

In the UK, there are health inequalities between minority ethnic minority groups and white British groups, but also between different ethnic groups and within them; the current terminology of ethnic groups does not take into consideration the heterogeneity within these groups. Access to primary care is generally equitable, but less so for other health services. People from ethnic minority backgrounds are more likely to report having poorer health and have poorer experiences of using health services compared to their white British counterparts.

The picture of health inequalities affecting different ethnic groups is complex across different conditions and is limited by a lack of good-quality data. For example, people from Bangladesh and Pakistan have the poorest outcomes across a range of indicators, together with those from Gypsy or Irish Traveller communities. Diabetes prevalence is higher among Black and South Asian groups, as is cardiovascular disease, with diabetes causing significant morbidity among these communities through diabetes complications. By contrast, the incidence of cancer is highest in the white British population [22–25, 29–36, 41].

What has the Covid-19 pandemic taught us in relation to ethnic minority groups?

These long-standing health disparities affecting ethnic minorities in the UK have been made acutely visible by the Covid-19 pandemic. Intensive Care National Audit and Research Centre figures from 1 September 2020 to 25 March 2021 showed that 24781 individuals

were admitted to intensive care with Covid-19, of whom 72% were white, 16% Asian, 5% Black, and 5% from other ethnic groups [42]. This is markedly different from 2011 census ward data (white 79.8%, Asian 11.2%, Black 5.0%, other 1.4%) [42]. Black and Asian individuals with diabetes in the UK were over-represented among those with Covid-19 receiving advanced respiratory support [42]. Public Health England later highlighted that deaths from Covid-19 among people from ethnic minority groups were 2–4 times higher than those among white counterparts [43, 44]. Disparities for some improved during the second wave. An analysis of a population-level ONS dataset reported that Black ethnic groups saw no increased risk of death from Covid-19 compared to white populations, but for South Asians the risk of poor Covid-19 outcomes was exacerbated [45].

Several reasons for these ethnic differences have been considered, including a higher prevalence of comorbidities associated with poor Covid-19 outcomes (e.g. type 2 diabetes among British South Asians, obesity), greater social deprivation, large multigenerational households, differences in occupational risk, and delayed access to healthcare, which all disproportionally affect ethnic minority groups [46]. SAHF summarizes these potential factors causing disparities in its Covid-19 and ethnic minority population report (Figure 68.2) [47].

Unpicking the causes of ethnic inequalities in Covid-19 outcomes, but also extending these to other health conditions including long-term non-communicable diseases such as diabetes, is difficult. Current evidence suggests it will be a complex interplay of factors that can be broadly categorized into structural (e.g. multigenerational housing, low income, working in healthcare or key worker roles, etc.) and biological (i.e. increased prevalence of long-term conditions) reasons. These potential explanations must be considered in the context of the wider determinants of health, including structural discrimination and racism [47].

Structural racism can reinforce inequalities among ethnic groups, for example in housing, employment, and the criminal justice system, which in turn can have a negative impact on health. Racism and discrimination can also have a negative impact on the physical and mental health of people from ethnic minority groups [41, 47].

The pandemic has overwhelmingly highlighted health inequalities and the urgent need for action to prevent and manage ill health in ethnic minority communities; this will include cross-government and health system strategies and policies for reducing health inequalities, and initiatives to tackle wider socioeconomic and structural inequalities that drive them [47].

The relationship between culture, discrimination, and impact on diabetes care

There is a large body of literature highlighting the link between reported racism and health and well-being. This is particularly striking when it comes to the health of children and young people [48–50]. A 2019–2020 audit reported that Black and South Asian children have higher HbA_{1c} and are significantly less likely to use diabetes technology such as insulin pumps and continuous glucose monitoring than White children [51]. In another survey of over 21 000 people with diabetes, those of South Asian origin had higher HbA_{1c} and higher blood pressure compared to the majority population [52]. Furthermore, despite glycaemic management being compromised, South Asians were less likely to use insulin (4.7% vs 7.1%) [52]. Another review also concluded an increase in mortality, end-stage complications, and poorer quality of care for people with diabetes [52]. Following adjustment for confounders such as smoking rates, socioeconomic status, household income, years of education, and body mass index (BMI), most of the ethnic differences became non-significant. However, in Black and Hispanic Americans and UK Asians, an increased risk of end-stage renal disease was still seen. Additionally, Black and Hispanic Americans had an increased risk of retinopathy. Specific health disparities arising from the provision of healthcare to those of a specific religion (such as people with diabetes and Muslim background) are widespread [53].

The necessity to address these concerns in relation to diabetes was well articulated in the Transcultural Diabetes Care in the US statement from the American Association of Clinical Endocrinologists [50]. Its models of diabetes care started from a consideration of diabetes risk factors for complications and led to the creation of models of care for each of the main ethnic groups reviewed: African Americans, Latinos, Asian Americans, and Native Americans. The main focus was on addressing important differences among the ethnic and cultural backgrounds of each individual [50]. There is a pressing need for this approach to be adopted to the needs of a people with diabetes, as data clearly show poorer outcomes in certain ethnic groups.

Specific cultural considerations when considering diabetes management

Dietary habits

Food has a deep cultural impact and plays a significant social role in sustaining tradition and social relationships. Therefore, altering diet in migrant communities can be challenging. Moreover, barriers to change may prevent the adoption of dietary advice by healthcare workers; if healthcare professionals are not culturally competent, their advice to avoid certain traditional foods can be perceived as dismissive of the South Asian diet [29]. There are only a few dietary intervention trials among South Asians, and key results suggest enhancing carbohydrate and fat quality in diet plans, with particular increase in protein intake to improve serum insulin, blood glucose, inflammatory markers, hepatic fat, and lipids [54].

Exercise and physical activity

There are no ethnicity-specific recommendations for exercise; however, South Asians have lower levels of physical activity relative to other populations [55, 56]. Studies comparing metabolic effects of exercise in South Asian and white European cohorts have shown differences: South Asian adults need to undertake nearly 232 minutes of moderate physical activity per week compared to 150 minutes for white Europeans to acquire similar benefits [55]. Barriers to physical activity in South Asians include lack of time outside long working hours, fear of racial harassment or abuse while exercising, expectations to remain at home, carer commitments, fear for personal safety, lack of same-gender venues, and concerns over the acceptability of wearing Western exercise clothing for women. However, attitudes to exercise in South Asians appear to be changing, albeit slowly [56].

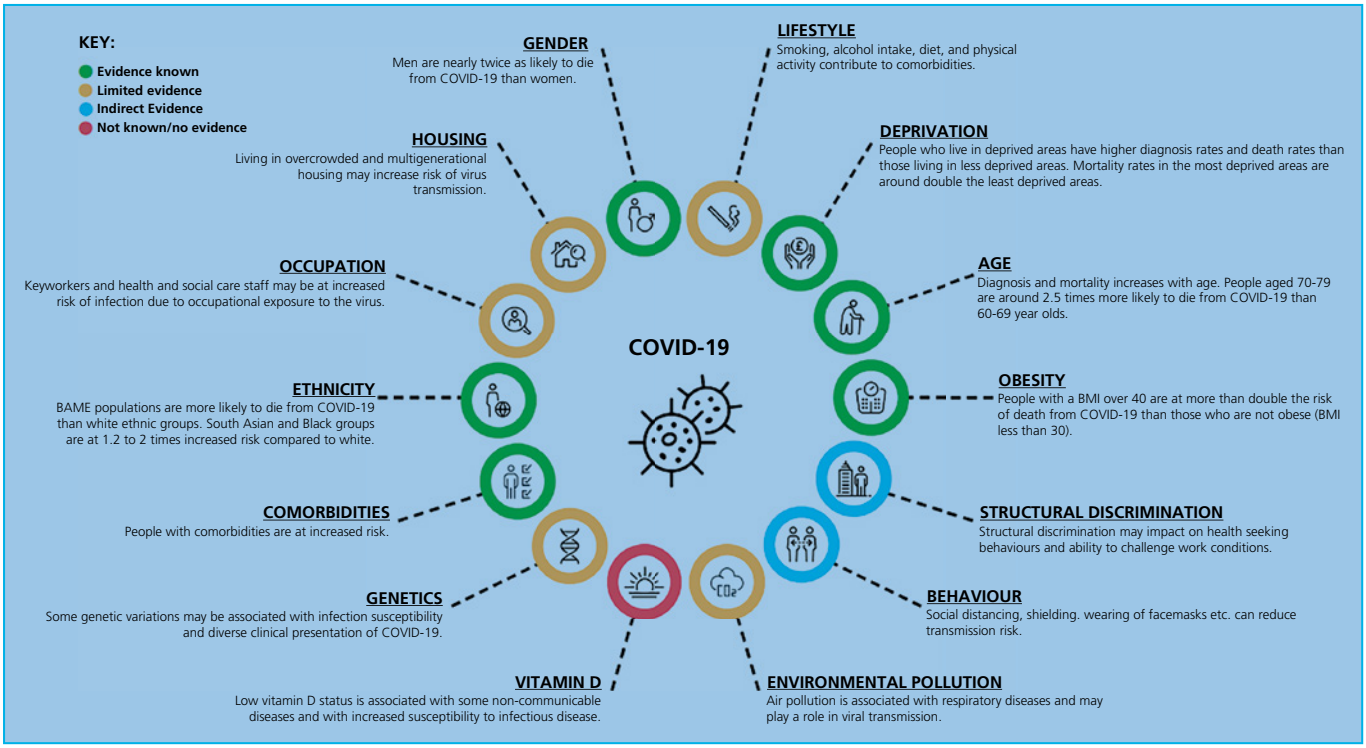

Figure 68.2 Factors associated with Covid-19 transmission and mortality. Source: Reproduced by permission from Khunti et al. (n.d.) [47].

Structured education

Structured education is integral to better diabetes management, as it enhances empowerment and autonomous self-management care [57]. For type 2 diabetes, diabetes education programmes currently available in the UK include Diabetes Education and Self-Management for On-going and Newly Diagnosed (DESMOND) and the eXPert Education versus Routine Treatment (X-PERT) diabetes programme; the former is validated in South Asian populations and has been developed for the Urdu-speaking South Asian community [29].

The Promotion Of Physical activity through structured Education with differing Levels of ongoing Support for people at high risk of type 2 diabetes (PROPELS) trial reported that ethnicity may influence the extent to which behavioural and demographic factors have impacts on physical activity and sedentary behaviour [58]. Once again, it is integral to overcoming these barriers that efforts are made to adapt screening and lifestyle interventions specifically to ethnic minority groups, such as South Asians. However, this remains challenging due to low levels of recruitment, retention, and follow-up in research trials. A feasibility study emphasized the value of community and faith centre-based screening and educational interventions in lowering the risk of type 2 diabetes among South Asians residing in the UK [59].

Impact of religious rituals on diabetes management

Fasting and feasting

Religious fasting is an important aspect of life for many South Asians, especially Muslims. The nature of abstaining from food during the day has implications for those people living with diabetes, particularly if the fasting period is prolonged, involves the abstinence of fluid as well as food, and involves continuous periods, such as weekly or over the month of Ramadan.

Specifically, for people living with diabetes religious fasting can increase the risk of hypoglycaemia, dehydration, postural hypotension, and ketoacidosis [60]. In addition to these risks, for Muslims the month of Ramadan needs to be viewed as both periods of fasting and feasting at the end of fast, which can lead to the risk of hyperglycaemia and weight gain, potentially worsened by reduced physical activity during the day [61].

While religious fasting is often associated with Muslims only, other faiths also practise fasting. Hindu fasts are distinctive owing to their day-long nature compared with the month-long fasts of Ramadan [62]. For Jains living with type 2 diabetes, most high-risk fasts may be discouraged in those taking any glucose-lowering therapy, while most low-risk fasts can be practised with an appropriate medication regimen and dose adjustments. People belonging to Judaism, Orthodox Christians, and the Baha'i faith also practise fasting, although these fasting periods are less frequent and spread out through the year.

Much of the evidence surrounding religious fasting and diabetes comes from studies during the Muslim month of Ramadan. Fasting in Ramadan is one of the five pillars of Islam and is considered a religious obligation for all Muslims, with some exceptions. Observing Ramadan fasts involves abstinence from food and drink between the hours following dawn (*suhoor*) to dusk (*iftar*); the duration of fasting might vary from 10 to 20 hours depending on the geographical location and season [63].

Although Ramadan observance is mandatory, religious exemptions to fasting include pregnancy, lactation, travelling, or any acute or chronic conditions where fasting might predispose the person to health risks [64]. Diabetes is considered a risk state for people fasting during Ramadan, particularly if there is risk of hypoglycaemia, glucose levels are not on target, or there is evidence of diabetes complications [65]. However, most Muslim people with diabetes do not consider themselves to be unwell and therefore would wish to fast during Ramadan as a declaration of their faith, as well as a sociocultural event to develop relationships with family and friends. Subsequently, many choose to fast despite medical advice against fasting [66].

Ramadan fasting involves prolonged hours of abstinence from food and fluid, often followed by an indulgent feast-like end-of-fast meal, for 29–30 consecutive days. Hence, those Muslims living with diabetes are at risk of hypoglycaemia, hyperglycaemia (including the increased risk of diabetic ketoacidosis and hyperosmolar hyperglycaemic state), dehydration, and thromboembolic events by undertaking these Ramadan fasts [60].

For those with diabetes and a desire to fast, there exists a need to manage their diabetes effectively during Ramadan. Specific structured education programmes focusing on Ramadan could provide clinical benefits and enhanced quality of life for individuals with type 2 diabetes [63, 67, 68]. Healthcare professionals should appreciate the impact of Ramadan fasting on the health of individuals with a Muslim background living with diabetes. By appreciating the risks, they will be able to discuss them openly with these individuals. At the same time, they should appreciate that some Muslims may wish to continue to fast despite understanding the risks. In this scenario, healthcare professionals should be able to support and manage these people in a non-judgmental way to reduce their risks and allow them to fast as safely as possible. Consequently, healthcare professionals must be knowledgeable and culturally competent about the basics of and exemptions to Ramadan fasting, and the treatments and procedures that invalidate fasting [69–72].

People with diabetes should receive a pre-Ramadan assessment at least 1–2 months before Ramadan by their diabetes team. Specific programmes such as A Safer Ramadan by DESMOND and the New Safer Ramadan eLearning module from Effective Diabetes Education Now (EDEN) provide training to help healthcare professionals be better equipped to support and manage people with diabetes who wish to fast [73–75].

Various guidelines are available, including the South Asian Health Foundation's guidelines for managing diabetes in Ramadan, which expand further on adjustments of medications for safe Ramadan fasting, risk stratification for fasting, and when to break the fast (Table 68.6) [63]. Box 68.1 presents a case study on diabetes and Ramadan to exemplify the issues and principles in managing people with diabetes who wish to fast, including risk stratification and medication adjustments during Ramadan.

Pilgrimage

Pilgrimages or spiritual journeys to a place of worship are practised in a number of faiths. Often this means that UK people with diabetes will travel to warmer climates to perform spiritual rituals practised outdoors in the heat over long periods of time, as well as walking long distances. Worldwide pilgrims may bring illnesses

Table 68.6 International Diabetes Federation/Diabetes & Ramadan International Alliance risk categories for people with diabetes who fast during Ramadan.

Risk category	Characteristics of the person with diabetes	Comments
Category 1: Very high risk	One of more of the following: • Severe hypoglycaemia within the 3 months prior to Ramadan • DKA within the 3 months prior to Ramadan • Hyperosmolar hyperglycaemic coma within the 3 months prior to Ramadan • History of recent hypoglycaemia • History of hypoglycaemia unawareness • Suboptimally managed type 1 diabetes • Acute illness • Pregnancy in pre-existing diabetes, or GDM treated with insulin or SUs • Chronic dialysis or CKD stage 4 and 5 • Advanced macrovascular complications • Old age with ill health	If person with diabetes insists on fasting then they should: • Receive structured education • Be followed by a qualified diabetes team • Check their blood glucose regularly (SMBG) • Adjust medication dose as per recommendations • Be prepared to break the fast in case of hypo- or hyperglycaemia • Be prepared to stop the fast in case of frequent hypo- or hyperglycaemia or worsening of other related medical conditions
Category 2: High risk	One or more of the following: • Type 2 diabetes with sustained hyperglycaemia above target[a] • optimally-managed Type 1 diabetes • optimally-managed Type 2 diabetes on MDI or mixed insulin • pregnant Type 2 diabetes or GDM managed by diet only or metformin • CKD stage 3 • Stable macrovascular complications • People with comorbid conditions who present additional risk factors • People with diabetes performing intense physical labour • Treatment with drugs that may affect cognitive function	
Category 3: Moderate/low risk	Optimally-managed type 2 diabetes treated with one or more of the following: • Lifestyle therapy • Metformin • Acarbose • Thiazolidinediones • Second-generation SUs • Incretin-based therapy • SGLT-2 inhibitors • Basal insulin	People who fast should: • Receive structured education • Check their blood glucose regularly (SMBG) • Adjust medication dose as per recommendations

[a] The level of glycaemia is to be agreed between doctor and person with diabetes according to a multitude of factors.
CKD, chronic kidney disease; DKA, diabetic ketoacidosis; GDM, gestational diabetes; MDI, multiple-dose insulin; SGLT-2, sodium–glucose cotransporter 2; SMBG, self-monitoring of blood glucose; SUs, sulfonylureas.

associated with the countries of origin to the often-overcrowded environments of pilgrimages, which can put people with diabetes at increased risk of infection.

The main risks associated with pilgrimage for people with diabetes include risks of infection, hypoglycaemia, poor access to adequate nutrition and water (resulting in hypoglycaemia, hyperglycaemia, or dehydration), heat exhaustion and heat stroke, foot ulcers, exertional angina, and the need to ensure adequate medical supplies.

Preparations for pilgrimage for people with diabetes require the following:

- Pre-pilgrimage travel consultation. This will allow any necessary medication adjustments and sick-day rules to be decided on.
- Adjustments of insulin timings depending on the travel time zone.
- Awareness of symptoms of hypoglycaemia and its management. A good source of information about longer travel journeys and timings of insulin can be found at https://www.diabetes.org.uk/guide-to-diabetes/life-with-diabetes/travel
- Foot checks and advice about footwear and prevention of foot ulcers.
- Ensuring sufficient medical supplies and discussion around storing insulin and carrying diabetes emergency kits.
- Advice regarding wearing identifiable medical wristbands.

Research priorities

There have been recent efforts to include more participation of people from ethnic minority groups with type 2 diabetes in clinical trials. Improving participation and reviewing research outcomes in these groups, including specific medications, will allow for more tailored guidelines for ethnic minority groups. However, despite these efforts, there remains an ongoing problem of small cohort sizes and lack of adequate data pertaining to these populations, which hinders prospects for the significant subgroup analyses that are important for ethnic susceptibility and guiding ethnicity-specific guidelines and management.

The barriers to recruitment and retention of research participants include lack of awareness about the significance of research within the community, perceived stigma around research topics, scepticism regarding study purpose and protocols, cultural

Box 68.1 Case study: diabetes care during Ramadan

Kabir Ali
- 64-year-old man.
- Type 2 diabetes for 16 years.
- Taxi driver.
- Previous laser therapy for diabetic maculopathy.
- BMI 28.2 kg/m^2.
- Non-smoker.

Drug history
- Atorvastatin 10 mg at night, ramipril 10 mg once daily, indapamide 2.5 mg once daily.
- Metformin 850 mg three times daily, gliclazide 160 mg twice daily, dapagliflozin 10 mg once daily.

Clinical data
- Blood pressure 136/84 mmHg.
- Total cholesterol 5.2 mmol/l, low-density lipoprotein (LDL) cholesterol 2.7 mmol/l, high-density lipoprotein (HDL) cholesterol 1.0 mmol/l.
- HbA_{1c} 63 mmol/mol (7.9%).
- Creatinine 98 µmol/l.
- Estimated glomerular filtration rate (eGFR) 64 ml/min.

Initial thoughts
- There will be no intake of lunch or fluid intake between dawn and sunset. It will therefore be prudent to move the antihypertensive therapies to iftar.
- Gliclazide could cause hypoglycaemia with no lunch (Table 68.7).
- A change to metformin 1000 mg twice daily could be justified as there is little or no benefit from increasing its dose above 2000 mg total dose daily.
- The dapagliflozin dosing does not need to be altered as there is only a mildly diuretic action.
- The National Institute for Health and Care Excellence (NICE) advised daily dose of atorvastatin for primary prevention is 20 mg, so there is an opportunity to increase the dose.

Table 68.7 Changes to treatment in Ramadan.

Pre-Ramadan treatment	Ramadan treatment
Breakfast time: ramipril 10 mg, indapamide 2.5 mg, metformin 850 mg, gliclazide 160 mg, dapagliflozin 10 mg	Suhoor: metformin 1000 mg, gliclazide 80 mg, dapagliflozin 10 mg
Lunch: metformin 850 mg	No oral intake during fast
Evening meal: metformin 850 mg, gliclazide 160 mg	Iftar: indapamide 2.5 mg, metformin 1000 mg, gliclazide 160 mg
Pre-bed: atorvastatin 10 mg	Pre-bed: atorvastatin 20 mg, ramipril 10 mg
	A glucagon-like peptide 1 (GLP-1) receptor agonist or dipeptidyl peptidase 4 (DPP-4) inhibitor instead of gliclazide would reduce the risk of hypoglycaemia and provide weight loss benefit

Box 68.1 (Continued)

Key principles
- Pre-Ramadan counselling should include all aspects of care and specific changes in medications that may be required.
- Consider a *mock fast* over a weekend, for example, to check that changes in medications advised suit the reality of fasting.
- Encourage safe fasting at all times, including being guided by the risk to the person with diabetes.
- Specific attention should be given to avoid hypoglycaemia and observe sick-day rules.
- Discuss the specific indications for breaking the fast, e.g. hypoglycaemia, hyperglycaemia cut-offs, and signs of dehydration.
- Advise regular glucose monitoring throughout the fast.
- Ensure good fluid intake outside of fasting hours.
- Discourage feasting habits after the fast, which will lead to hyperglycaemia and weight gain.

Review post-Ramadan (at next routine review) to ascertain the safety of current practice and plan for next year's Ramadan.

insensitivity, competing priorities, and influences pertaining to family, community, and cultural preferences restricting the inclusion of Asian subgroups into trials. Worryingly, compared to white Europeans or individuals of other ethnicities, there is a significantly higher number of South Asian people who are excluded from participation in research due to language barriers [76].

Therefore, it is of the utmost importance and urgency that researchers are trained to be culturally competent and have the essential culturally sensitive techniques to recruit and retain people from ethnic minority groups. Various strategies have been proposed to facilitate South Asian participation in clinical trials (Figure 68.3).

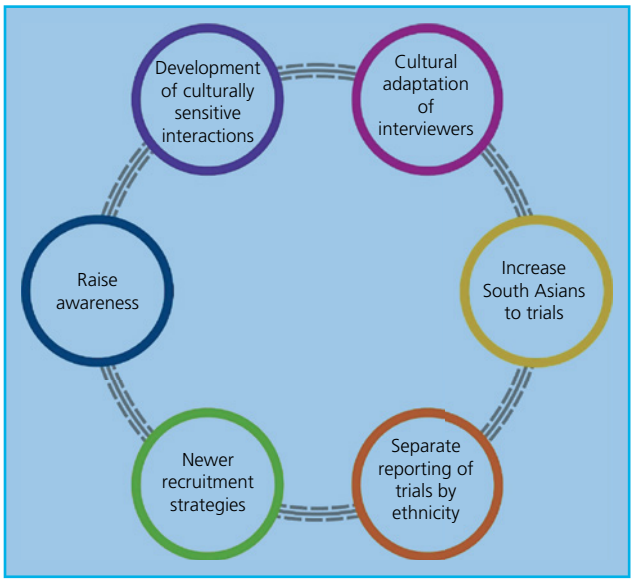

Figure 68.3 Strategies proposed to enhance participation from ethnic minority groups in clinical research trials. Source: Reproduced by permission from Hanif et al. 2021 [29].

Conclusion

Even before the impact of Covid-19 on ethnic minority groups, we appreciated that people of Black and South Asian ethnicity were at higher risk of type 2 diabetes and its complications compared to white Europeans. Recent events including the global Covid-19 pandemic have simply reminded us of the ongoing health inequalities and have continued to widen them for ethnic minority groups.

By understanding the relevance of ethnicity and culture on beliefs and daily practices, which can affect health and disease management, we can begin to appreciate the reasons for health inequalities and be better equipped to reduce health inequalities and improve health outcomes, including for people with diabetes.

The real take-home message is for us all to become culturally competent as individual healthcare providers and as healthcare systems as a whole, so that we can continue to individualize the management of people with diabetes and improve their outcomes.

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69 Diabetes in Childhood

Jennifer M. Ikle, Ananta Addala, and David M. Maahs
Division of Endocrinology, Department of Pediatrics, Stanford University, Stanford, CA, USA

Key points

- An estimated 1.1 million children have diabetes worldwide; over 125 000 new cases are diagnosed annually and the incidence has been increasing by up to 5% annually over decades.
- Type 1 diabetes accounts for almost all cases in children younger than 10 years, for >90% among older children of European ancestry, and for 20–70% of diabetes in children older than 10 years from other ethnic groups.
- In the last decade, the incidence and prevalence of paediatric type 2 diabetes have markedly increased and should be considered in the differential diagnosis of new-onset diabetes in children and adolescents.
- The presence of two or more islet autoantibodies predicts the development of diabetes in those less than 10 years in most cases; despite an enormous research effort, prevention of type 1 diabetes is still elusive.
- Diabetes in children is diagnosed based on polyuria, polydipsia, weight loss, fatigue, and random blood glucose >200 mg/dl (11.1 mmol/l). Oral glucose tolerance testing is rarely needed.
- The classical presentation of diabetic ketoacidosis (DKA) in a thin, dehydrated child with Kussmaul breathing, abdominal pain, vomiting, and impaired neurological status is present at diagnosis in approximately 30% of cases in high-income countries.
- There are significant differences in the management of DKA in children, compared with adults, with the primary focus being on prevention of the cerebral oedema.
- After diagnosis, childhood diabetes is managed in the outpatient setting by a team including a paediatric endocrinologist specializing in diabetes, a diabetes nurse educator, a dietitian, a paediatric social worker, and/or a paediatric psychologist trained in childhood diabetes.
- Diabetes technology, such as continuous glucose monitors and insulin pumps, is associated with improved glycaemic and psychosocial outcomes, and should be considered in all children and adolescents with type 1 diabetes.
- Disparities in diabetes technology use and glycated haemoglobin (HbA_{1c}) exist by socioeconomic status and race/ethnicity.
- Telemedicine is an effective means of delivering paediatric diabetes care and can supplement in-person visits.
- In-depth initial and continuing education of parents and children in the self-management of diabetes is the cornerstone of lowering the risk of acute and long-term complications.
- Insulin pump or basal bolus multiple daily injections are the standard of insulin therapy in children.
- Nutrition planning should be based on a carbohydrate counting or exchange system; the macronutrient and micronutrient composition of the diet is similar to that for healthy children without diabetes.
- While regular exercise is recommended for all children with diabetes, it requires careful planning of insulin and nutritional management to prevent severe hypoglycaemia.
- Severe hypoglycaemia is largely preventable, but is still the most common serious complication of childhood diabetes.
- Healthcare providers should equip families with the tools necessary to avoid dehydration, uncontrolled hyperglycaemia or DKA, and hypoglycaemia during routine infections.
- HbA_{1c} levels below 53 mmol/mol (<7.0%) are the target currently recommended and achievable by most children and adolescents; the gap between recommended and actual HbA_{1c} levels is the widest among adolescents.
- Age-specific psychological care should include screening for and treatment of family dysfunction, developmental maladjustments, and communication problems, disordered eating and sleep patterns, as well as psychiatric disorders both in children and their care providers.
- All children with diabetes should be screened at an appropriate age and duration of diabetes for dyslipidaemia, microalbuminuria, elevated blood pressure, retinopathy, coeliac, and thyroid disease.

Spectrum of diabetes in children

In Europe and North America, 1 in 300 children develops type 1 diabetes by the age of 20 years [1]. There are an estimated 1.1 million children and adolescents aged 0–19 years living with type 1 diabetes, with 128 900 new cases diagnosed each year as of 2019 [2]. The incidence and prevalence rates are highest in Europe (31.1/100 000 per annum and 269.5/100 000, respectively) and the lowest in Africa (10.1/100 000 per annum and 25.8/100 000, respectively) [1]. Diabetes is a heterogeneous disease at any age. Newborn babies and infants rarely develop the disease (1 in 250 000 in those younger than 6 months) and in those cases the aetiology is not autoimmune, but usually monogenic (Chapter 20). From the age of

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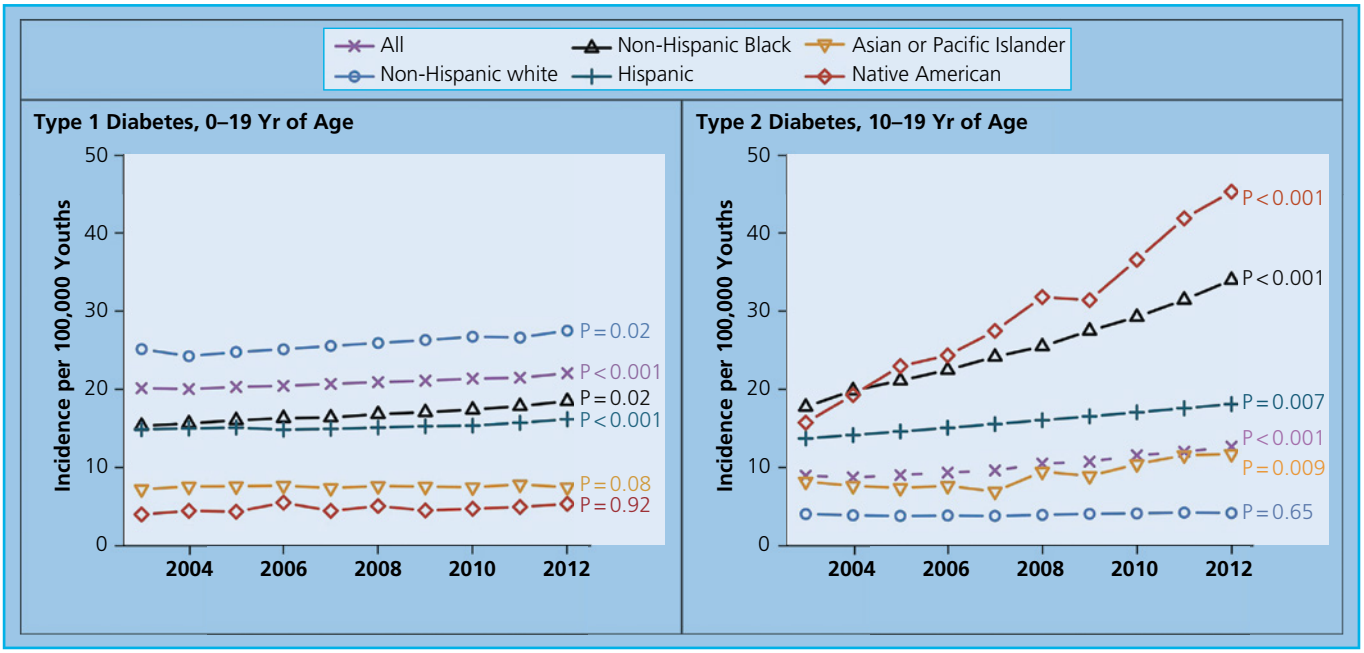

Figure 69.1 Diabetes incidence in youths less than 20 years of age. Source: Data from Mayer-Davis et al. 2017 [3].

9 months to 10 years, almost all diabetes is caused by islet autoimmunity (Chapter 14). The incidence of type 1 diabetes has been increasing in the last decade, with the greatest rise in incidence in children and adolescents from racial and ethnic minority groups. In addition to the rise in type 1 diabetes incidence, in the last decade there has been a marked rise in the incidence and prevalence of type 2 diabetes (Figure 69.1) [3]. Measurement of autoantibodies to insulin, glutamic acid decarboxylase (GAD65), islet tyrosine phosphatase 2 (IA-2), and zinc transporter 8 (ZnT8) at diagnosis and examination for signs of insulin resistance may be necessary to determine the diagnosis and long-term treatment.

This chapter focuses on the practical aspects of the management of type 1 diabetes in children, while Chapter 69 addresses management of type 1 diabetes in adolescents and transition to adult care. Management of type 2 diabetes in children is increasingly important, as the incidence and prevalence of type 2 diabetes in this age group have been increasing. In addition, greater rates of morbidity and mortality are observed in paediatric type 2 diabetes when compared to type 1 diabetes. Female, adolescent, and non-Hispanic Black youths with type 2 diabetes have excess mortality, whereas short-term excess mortality was not observed in youths with type 1 diabetes [4–6]. However, life expectancy remains 8–13 years shorter and cardiovascular disease continues to be the leading cause of morbidity and mortality in type 1 diabetes [7], and earlier age at type 1 diabetes diagnosis is associated with shorter lifespan [8, 9]. Chapters 15 and 20 provide a description of type 1b diabetes, where the clinical presentation is as in type 1a diabetes but without evidence of islet autoimmunity, and monogenic diabetes, respectively. The epidemiology and aetiology of type 1 diabetes are addressed in Chapter 4 and Chapter 14, respectively. The temporal changes in incidence rates over the last 15 years vary by country. While type 1 diabetes incidence rates continue to rise steadily in many countries, some countries, such as Finland, Norway, Sweden, Denmark, and parts of the UK, are showing signs of a slowing in the rise [10–13]. Elimination of the environmental trigger(s) responsible for this epidemic would be the most efficient approach to primary prevention; however, there is lack of consensus about which environmental factors initiate and promote islet autoimmunity [10–14]. Efforts to prevent or delay type 1 diabetes have been recently reviewed elsewhere [15].

After the initiation of islet autoimmunity, most people have a long pre-clinical period that offers an opportunity for secondary prevention of the progression to clinical diabetes. The presence of more than one of the autoantibodies combined with susceptibility to human leucocyte antigen (HLA)-DR, DQ genotypes identifies those at high risk of developing diabetes. There may be a 'point of no return' in the autoimmune destruction of the islets, rendering some interventions effective only at the earlier stages of the process. In most individuals with persistence of islet autoantigens, progression to diabetes occurs within 10 years. A period of mild asymptomatic hyperglycaemia, detectable by oral glucose tolerance testing (OGTT) or glycated haemoglobin (HbA_{1c}) [15, 16] may precede by months or years overt insulin dependence among those with islet autoantibodies. Intervention at this *dysglycaemic* stage may also theoretically preserve endogenous insulin secretion and reduce the acute and long-term complications of type 1 diabetes. Preservation or regaining of residual insulin secretion after diagnosis of diabetes might also help, but the immunomodulatory agents used so far in tertiary prevention carry unacceptable long-term risks.

The growing understanding of the heterogeneity of paediatric diabetes in the last decade has brought new challenges to diabetes management in children. In particular, these challenges include appropriate identification of diabetes type and addressing disparities in diabetes care management and outcomes [17–20]. The modern obesogenic environment has resulted in the rising prevalence of both obesity in paediatric type 1 diabetes and the incidence of paediatric type 2 diabetes [21–24]. The rates of obesity and overweight are higher in children and adolescents with type 1 diabetes than in the general population and therefore nutritional and exercise interventions should be considered in the treatment of all paediatric diabetes [25, 26].

In the last half decade, data have demonstrated marked disparities in diabetes management and outcomes in minority racial/ethnic and lower socioeconomic groups [17–19]. The degree of these disparities varies by country, but they are present in all countries with regard to diabetes technology use, HbA_{1c}, and diabetes-related complications [17, 27]. Social determinants of health are defined as the economic, environmental, political, and social conditions in which people live that play a significant role in health outcomes and are considered to be, in part, responsible for health inequity worldwide [28, 29]. Strategies to tailor treatment of type 1 diabetes in the psychosocial context of the young person and their family include [28]:

- Understanding the role of social determinants of health in diabetes management and outcomes.
- Assessing food, housing, and the financial and legal security of the family.
- Evaluating the impact of racism and discrimination on the young person and their family.
- Being apprised of and referring appropriately to community resources.
- Providing family and youth support with lay health coaches or community workers.

Addressing these disparities along with the continued innovation of diabetes technology is an important step towards equitable care for all children and adolescents with diabetes.

Manifestation, diagnosis, and initial treatment

Clinical presentation and diagnosis

The cardinal symptoms at the diagnosis of diabetes include polyuria (96% of children, often with nocturia or bed-wetting), polydipsia, weight loss (61%), and fatigue [30]. The classic presentation of diabetic ketoacidosis (DKA) in a thin, dehydrated child with Kussmaul breathing, abdominal pain, vomiting, and impaired neurological status affects less than half of cases presenting in high-income countries today [31–33]. With the increasing community recognition of diabetes, most children present with milder hyperglycaemia of shorter duration; however, 75% of the children (63% below age 5 years) have the symptoms for more than two weeks, suggesting that the diagnosis could be made earlier in many cases. Very young children may have less specific presentations, for example with vomiting or rapid breathing, often in the setting of a concurrent illness or infection. Diabetes should always be considered in ill children; urine or blood testing for glucose and ketones leads to an early diagnosis and may prevent DKA and hospitalization. Recognition of early diabetes symptoms is critical, as many children admitted with severe DKA have missed or delayed diagnosis by other healthcare providers [30].

While insulin infusion and intravenous fluids are required for a minority of new-onset cases of diabetes, many children who are newly diagnosed may spend several days admitted to the hospital. These hospitalizations could be avoided if safe outpatient alternatives and adequate reimbursement existed for this initial care. The majority of centres in the USA continue to require a several-day hospital stay for new diabetes diagnosis, to allow for family and caregivers to acquire the necessary knowledge base and practise the daily skills involved in diabetes care [34]. However, these hospitalizations have both economic and emotional impacts – both on the healthcare system as a whole and on individual families, who may travel, need childcare, be underinsured, and so on. Because of these considerations, some institutions have adapted alternative models of diabetes education and recent studies have shown that outpatient education results in lowering of healthcare costs without compromising medical care [35, 36].

The diagnostic criteria are the same in children and adults (Chapter 2). In a symptomatic child, plasma glucose ≥11.1 mmol/l (200 mg/dl) at any time of day, without regard to time since the last meal, or fasting plasma glucose ≥7.0 mmol/l (126 mg/dl) is diagnostic. Blood glucose results obtained using a glucose meter should be immediately confirmed in a laboratory, before the initiation of insulin treatment. By contrast, if marked hyperglycaemia and blood or urinary ketones are present, treatment is urgent; waiting another day to confirm the diagnosis may be dangerous if DKA is allowed to develop. In a well child, the diagnosis must not be based on a single plasma glucose test or borderline results obtained using a glucose meter. In such cases, it is reasonable to obtain the HbA_{1c} level; if this is normal, further monitoring of the fasting and/or two hours post-prandial blood glucose is recommended for several days. In children progressing to overt diabetes, hyperglycaemia after dinner is usually the initial abnormality detectable by self-monitoring of blood glucose at home. OGTT should not be performed if fasting, random, or post-prandial criteria are met, as it is unnecessary and excessive hyperglycaemia can result.

Hyperglycaemia detected incidentally or during acute infection, trauma, or other illness may be transient, especially if typical symptoms of diabetes are absent or equivocal. Non-diabetic causes of hyperglycaemia include stress, acute illness, and use of glucocorticoids and other medications [37]. The need for treatment or additional follow-up should be addressed on a case-by-case basis, as length, severity, and cause of hyperglycaemia will guide the next steps. There are some data suggesting that children with stress hyperglycaemia are more likely to develop diabetes in the future, but this has not been widely supported in the literature [38, 39].

The combination of antibody testing and genetics can also help to determine the diagnosis, particularly in children with mild or early presentations. Additionally, antibodies play an increasingly important role in differentiating type 1 diabetes and type 2 diabetes, as obesity is increasing and body habitus is no longer a reliable way to distinguish between these two pathologies. More than 80–90% of individuals with newly diagnosed type 1 diabetes have one or more anti-islet cell autoantibodies (islet cell antibodies, insulin autoantibodies, antibodies to the 65 kD isoform of GAD65, the IA-2 molecule, and ZnT8), and the presence of two or more autoantibodies is highly predictive of progression to overt diabetes [40, 41].

A majority of type 1 diabetes cases occur in individuals without a family history of the disease; however, individuals with a first-degree relative with type 1 diabetes have a 5% lifetime risk of developing type 1 diabetes, compared with a 0.3% lifetime risk for the general population. Monozygotic twins have a concordance rate of >50%, whereas dizygotic twins have a concordance rate of 6–10% [42, 43]. Genetic risk scores (GRS) are a growing tool to predict the development of type 1 diabetes, as well as distinguishing it from other forms of diabetes, such as monogenic diabetes or type 2 diabetes [44, 45]. Genetic factors can be complemented by environmental and other factors to improve predictability; one example of this is the combined risk score (CRS), which utilizes the GRS2 as well as family history and presence of autoantibodies and is more highly predictive of type 1 diabetes than any of those components when used alone [44, 46–49]. Improved predictability, particularly in the early stages of type 1 diabetes, will maximize the potential for intervention as potential preventive therapeutics are identified.

The possibility of other types of diabetes should be entertained in children who have negative diabetes autoantibodies and any of the following features:

- Diagnosis at <6 months of age.
- Autosomal-dominant family history of diabetes.
- Mild fasting hyperglycaemia that does not progress.
- Associated syndromic features.
- History of exposure to drugs known to cause β-cell toxicity or insulin resistance.

Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) may also be detected in a child with islet autoimmunity progressing to overt diabetes [50]. OGTT is rarely needed in prepubertal children. In older children, especially obese teenagers with equivocal symptoms, the OGTT may have a role in the earlier diagnosis of type 2 diabetes, IGT, and IFG.

Monogenic diabetes

While type 1 diabetes and type 2 diabetes have multifactorial aetiologies, monogenic causes of diabetes are also important causes of paediatric diabetes. This includes maturity-onset diabetes of the young (MODY) and neonatal diabetes mellitus. MODY is an autosomal, dominantly inherited form of diabetes that is characterized by an early age of onset (at least one affected family member with an onset before 25 years of age) and pancreatic β-cell dysfunction [51]. Mutations in the three most commonly associated genes (*HNF1A, HNF4A*, and *GCK*) can account for up to 95% of all MODY cases.

Neonatal diabetes mellitus is a heterogeneous disease defined as diabetes with onset during the first six months of life, with a monogenic cause identifiable in up to 85% of cases [52]. Mutations in the genes that comprise the pancreatic adenosine triphosphate (ATP)-sensitive potassium channels, *ABCC8* and *KCNJ11*, are the most common causes of neonatal diabetes mellitus, and cases due to these mutations are often responsive to oral sulfonylureas, potentially avoiding the need for insulin therapy [53]. If clinical presentation is typical for either MODY or neonatal diabetes mellitus, especially in antibody-negative individuals, genetic testing should be performed.

Diabetic ketoacidosis

The clinical presentation of DKA includes abdominal pain, nausea, and vomiting, which can mimic an acute abdomen. The children are mildly to moderately dehydrated (5–10%), may have Kussmaul respiration, and become progressively somnolent and obtunded. DKA results from absolute or relative deficiency of circulating insulin and a corresponding increase in the levels of counter-regulatory hormones, such as catecholamines, cortisol, glucagon, and growth hormone (Chapter 41). This combination leads to a catabolic state with increased glucose production by the liver and kidneys, increased lipolysis, ketogenesis with ketonaemia, and metabolic acidosis. Absolute insulin deficiency occurs in children with previously undiagnosed type 1 diabetes or in those with an established diagnosis through omission of or inadequate insulin regimens. Relative insulin deficiency occurs during acute illness and stress if the increase in counter-regulatory hormones is not balanced by an appropriate increase in insulin dosage.

DKA is defined by the triad of ketonaemia and/or ketonuria, acidosis (serum pH <7.3 and/or serum bicarbonate <15 mEq/l), and hyperglycaemia, although DKA can occur without hyperglycaemia if the individual is pre-treated at home or in another hospital [54]. The severity of DKA is typically categorized by the degree of acidosis:

- Mild: venous pH 7.2–7.3 or bicarbonate <15 mmol/l.
- Moderate: venous pH 7.1–7.2 or bicarbonate <10 mmol/l.
- Severe: venous pH <7.1 or bicarbonate <5 mmol/l.

Diabetic ketoacidosis at diagnosis of diabetes

In the USA, an average of 28% of individuals less than 20 years of age diagnosed with type 1 diabetes presented in DKA [31]. Globally and throughout the USA rates of DKA presentation vary, ranging from 19% to 58% on initial diagnosis, and correlating inversely with the local incidence of type 1 diabetes [32, 33]. DKA is more often found among younger children and in children with lower socioeconomic status who encounter barriers in accessing medical care [33, 55]. Intensive community intervention to raise awareness of the signs and symptoms of childhood diabetes among school teachers and primary care providers may help to reduce the prevalence of DKA at diagnosis.

Diabetic ketoacidosis in children with established type 1 diabetes

In two large cohorts of children with established type 1 diabetes, on average 4–7 per 100 developed DKA every year [56, 57]; however, nearly 60% of the DKA episodes occurred in 5% of children with recurrent events. Recurrent DKA was predicted by omission of insulin, suboptimal metabolic management, intercurrent gastroenteritis with dehydration, psychiatric and eating disorders, difficult family or social circumstances or limited access to medical care, and the use of insulin pump therapy. Recurrent DKA is more common in peripubertal or adolescent girls.

Treatment of ketoacidosis

Children with DKA should ideally be cared for in a unit with nursing staff trained in management of DKA in children, written guidelines for DKA management in children, and access to a laboratory capable of providing frequent and timely biochemical results. In 2020, the International Society for Paediatric and Adolescent Diabetes (ISPAD) released additional guidelines for consideration during the SARS-CoV-2 pandemic, recommending that in cases where intensive care unit (ICU) capacity may be limited, some children with mild and moderate DKA may be treated outside of the ICU without compromising care [58]. Hydration status should be assessed and fluid deficit and osmolality calculated to help guide fluid and electrolyte replacement. Serum electrolytes, glucose, blood urea nitrogen, creatinine, calcium, magnesium, phosphorous, and blood gas testing should be repeated every 2–4 hours or more frequently in severe cases. The calculations are shown in Box 69.1.

Children with DKA have a 5–10% deficit in extracellular fluid volume that has developed slowly and rapid or overzealous fluid replacement should be avoided, largely to minimize the risk of cerebral oedema. Initial volume expansion should occur over the first 1–2 hours with intravenous (IV) infusion of 10–20 ml/kg normal

Box 69.1 Calculations of anion gap, corrected sodium, and serum osmolality

Anion gap = $Na - (Cl + HCO_3)$

Corrected Na = measured Na + [(plasma glucose – 100 mg/dl) (1.6)/100]

Serum osmolality = 2(Na + K) + glucose/18 + blood urea nitrogen/2.8(mOsm/l)

Box 69.2 Estimate of 24-hour maintenance fluid volume

Estimation based on age:
- 0–2 years = 80 ml/kg
- 3–5 years = 70 ml/kg
- 6–9 years = 60 ml/kg
- 10–14 years = 50 ml/kg
- >15 years = 35 ml/kg

Estimation based on body weight:
- 100 ml/kg for the initial 10 kg body weight, plus
- 50 ml/kg for the next 10 kg body weight, plus
- 20 ml/kg for each additional kg body weight

For example, a child weighing 30 kg needs 1000 + 500 + 200 = 1700 ml maintenance water for 24 hours or 70 ml/h, not counting past or ongoing losses.

saline (0.9%) or Ringer solution. The bolus rarely needs to be repeated and should not exceed a total of 40 ml/kg over the first four hours of treatment. Subsequent fluid deficit replacement should occur over the next 48 hours using half to three-quarters of normal saline, in addition to electrolytes (Box 69.2). Hypotonic fluids (e.g. half normal saline) are typically used for continued fluid replacement, although a recent study found that among four arms of treatment, neither the rate of fluid repletion nor the salinity of the chosen fluids alters the risk of cerebral oedema [59].

Once blood glucose concentrations reach 250 mg/dl (14 mmol/l), 5–10% dextrose should be added to the IV solution to maintain the blood glucose concentration between 150 and 250 mg/dl (8–14 mmol/l) and avoid saline overload and hyperchloraemic acidosis.

Continuous IV insulin infusion (typically consisting of diluted regular insulin) at a dose of 0.05–0.1 units/kg/h should commence after the child has received initial volume expansion. An IV bolus of insulin is unnecessary and may increase the risk of cerebral oedema [54]. The insulin infusion should allow for a gradual decrease in blood glucose concentration by 50–100 mg/dl/h (2.8–5.6 mmol/l/h). If the blood glucose levels decrease too quickly or become too low before the acidosis has resolved, the IV dextrose concentration may be increased to 12.5% to prevent hypoglycaemia while continuing to correct the metabolic acidosis with insulin. Caution should be used when considering decreasing the infusion rate below 0.05 units/kg/h, as this is likely to prolong the time needed to suppress ketogenesis, but it may be clinically appropriate in severe or persistent hypoglycaemia. Bedside monitoring of blood ketones (β-hydroxybutyrate) is more helpful than blood gases in adjusting insulin and glucose infusion rates.

Total body potassium is usually depleted, but serum levels at presentation may be normal or high secondary to efflux of intracellular potassium into the extracellular space in the presence of acidosis. Similarly, serum phosphorus levels may be initially elevated only to fall rapidly, frequently leading to hypophosphataemia. Once the serum potassium is found to be normal or low, and urine output is confirmed, IV fluids should include 20–40 mEq/l potassium in the form of K acetate, K_2HPO_4, or a combination of these. Clinical problems resulting from low phosphorus levels have not been substantiated; however, severe hypophosphataemia (<1 mg/dl) should be treated. No more than half of the potassium replacement should be given as K_2HPO_4, because excessive phosphorous administration may result in hypocalcaemia and hypomagnesaemia following the suppression of parathyroid hormone. If hypocalcaemia develops, administration of phosphate should be decreased or stopped.

Severe acidosis is reversible with fluid and insulin replacement. Bicarbonate therapy may paradoxically cause central nervous system acidosis and hypokalaemia from rapid correction of acidosis and is a risk factor for cerebral oedema. Bicarbonate therapy is not recommended except in situations of cardiovascular collapse due to acidosis. If bicarbonate is considered necessary, 1–2 mmol/kg can be cautiously administered over 60 minutes in an intensive care unit setting.

Cerebral oedema

Cerebral injury is the major cause of morbidity and mortality in children with cerebral oedema, accounting for 60–90% of all deaths due to DKA while up to 10–25% of survivors have significant residual morbidity [54]. Neurological status must be monitored at frequent and regular intervals. Subclinical cerebral oedema occurs in most children with DKA. Severe clinical oedema affects 0.5–1% of the children and is fatal in over 20% [60]. Typically cerebral oedema occurs at 4–12 hours, but has been reported as late as 24–28 hours after the initiation of IV fluid treatment. Potential risk factors for symptomatic cerebral oedema in children include:
- Age <5 years old.
- More profound dehydration, hyperventilation, and acidosis at presentation.
- Bicarbonate therapy.
- Excessive and rapid fluid administration, especially if initial serum osmolality >320 mOsm/l or initial serum glucose >800 mg/dl (44 mmol/l).
- Rapid correction of glucose.
- Failure of serum sodium to rise as hyperglycaemia resolves.
- Initial IV insulin bolus or too early initiation of insulin infusion.

Signs and symptoms of cerebral oedema include headache, change in mental status or behaviour, incontinence, focal neurological findings, sudden normalization of heart rate in a previously tachycardic dehydrated child, or a worsening clinical course in a child with improved laboratory values. Bradycardia, hypertension, and irregular respiration (Cushing triad) are signs of greatly increased intracranial pressure. Early intervention is essential. Treatment includes administration of mannitol (1 g/kg over 30 min), decreasing fluid rate to 75% or less of maintenance rate, and elevation of the head of the bed. Mannitol therapy may need to be repeated. IV hypertonic saline has also increasingly been used as an alternative to mannitol, although there is variability in treatment approaches across institutions and between emergency versus critical care settings [61]. There remains a paucity of data comparing the two approaches [62, 63], but current guidelines allow for either approach [54]. Treatment should not be delayed for the purpose of imaging, and any necessary radiographic studies (such as head computed tomography [CT]), should be obtained after, rather than during, treatment of cerebral oedema [64].

Frequent monitoring of blood glucose levels should prevent hypoglycaemia. For acute hypoglycaemic episodes while on continuous insulin infusion, the insulin infusion may be temporarily discontinued for up to 15 minutes if necessary.

Transition to a subcutaneous insulin regimen

Children may be transitioned to an appropriate subcutaneous insulin regimen once DKA has resolved and they are able to eat. To prevent rebound hyperglycaemia, the insulin infusion should not be discontinued until 15–30 minutes after the first injection of

rapid-acting insulin has been administered. Long-acting insulin analogues achieve therapeutic levels sufficient to replace insulin infusion 4–6 hours after the injection. Bedside monitoring of blood ketones can help titrate insulin dose and prevent a relapse.

Hyperglycaemic hyperosmolar syndrome

Hyperglycaemic hyperosmolar syndrome (HHS) can occur in children, most often, but not exclusively, in the setting of type 2 diabetes, and is defined as follows [65]:

- Plasma glucose concentration 600 mg/dl (>33.3 mmol/l).
- Venous pH > 7.25 or arterial pH > 7.30.
- Serum bicarbonate >15 mmol/l.
- Negative or trace urine ketones or absent to small blood ketones.
- Serum osmolality >330 mOsm/kg.

Presentation of HHS can have a more insidious onset than DKA, and polyuria and polydipsia may continue until profound dehydration occurs, with approximately 50% of cases having altered consciousness or seizures. Compared to DKA, children with HHS need greater amounts of fluids to avoid intravascular collapse, which contributes to the mortality seen in HHS.

Approach to HHS treatment should include:

- Gradual decrease of sodium concentration, often by titrating the sodium content in fluids.
- Gradual decrease in glucose of 75–100 mg/dl/h (4.2–5.6 mmol/l/h) or less, after first few hours of therapy.
  - Initial treatment with bolus fluids causes a greater fall in glucose initially, but this should not persist.
  - Insulin therapy is delayed until glucose is falling less than 50 mg/dl/h (3 mmol/l/h) and should be initiated at 0.025–0.05 units/kg/h and adjusted to maintain a decrease in serum glucose of 50–75 mg/dl/h (2.7–4.1 mmol/l/h).
- Close monitoring including hourly checks of glucose, vital signs, hydration, and clinical status.
- Monitoring of serum electrolytes, blood urea nitrogen, creatinine, osmolality, and determination of intake/output balance every 2–3 hours, and phosphate and magnesium every 3–4 hours.
  - Treat hypokalaemia, hypophosphataemia, and hypomagnesaemia if they are present.
- Checking creatine kinase every 2-3 hours to monitor for rhabdomyolysis.

Complications of HHS include venous thrombosis associated with the use of central venous catheters, rhabdomyolysis, and malignant hyperthermia. Cerebral oedema is rarely seen. Children can have a mixed picture of DKA and HHS, and in these cases typically more fluids are given than usual for DKA, and insulin is started sooner than in HHS, but treatment should be based on the individual clinical presentation [54, 65].

Paediatric ambulatory diabetes care

Diabetes is primarily managed in the outpatient setting by a team including a paediatrician specializing in diabetes, a certified diabetes educator or diabetes nurse, a dietitian, a paediatric social worker trained in childhood diabetes, and/or a paediatric psychologist with knowledge of childhood diabetes and chronic illness. In communities with low population density and low prevalence of childhood diabetes, such a care team may not be available and care will primarily be provided by the child's primary care physician. In these instances, these physicians should work closely with and have access to a regional diabetes care team. When available, telemedicine utilizing two-way video-computer technology and local medical staff offers a way for more efficient and effective care from afar [66–74]. Healthcare providers and the diabetes care team must always be cognizant of and sensitive to the cultural needs and barriers to care that may arise with minority children of recent immigrants. When providers do not speak the preferred language of the family, interpreters should be utilized in care delivery.

Initial education

Initial education should provide a basic understanding of the pathophysiology of diabetes and its treatment to ensure that families feel confident in providing diabetes care at home (Table 69.1).

At many institutions, initial education at time of diagnosis occurs in an inpatient setting regardless of whether or not the child presents acutely ill in DKA. In some centres with appropriate outpatient resources, initial diabetes education and initiation of insulin therapy can occur in the ambulatory setting, which has been shown to be cost-effective. The introduction of continuous glucose monitoring (CGM) shortly after type 1 diabetes diagnosis is well received by children and adolescents and their families and is associated with improvements in HbA_{1c} [76, 77]. Therefore, introduction of diabetes technology and, if possible, offering CGM shortly after diagnosis should be considered in the initial education.

Continuing education

In the first six months following diagnosis, close contact in the form of frequent outpatient visits, home visits, telephone communication, and other methods of communication is essential for addressing the frequently changing requirements during this time (Table 69.2) [75].

Diabetes education is a continuous process and must be repeated to be effective. It must be adapted and appropriate to the age of the child. Infants and toddlers often have unpredictable eating and activity patterns. There is commonly more difficulty in distinguishing normal behaviour from mood swings related to hypoglycaemia or hyperglycaemia. Needle phobia can present a significant issue with the perception of pain inflicted by the caregiver. Hypoglycaemia is more common in this age group and the prevention, recognition, and management of hypoglycaemia are a priority [78, 79]. Fear of hypoglycaemia is a well-recognized barrier to achieving optimal glycaemic targets and meeting exercise goals, thereby having impacts on long-term diabetes-related complications including cardiovascular morbidity [80]. CGM use is associated with an improvement in time spent in range without an increase in

Table 69.1 Initial education curriculum.

Explanation of how the diagnosis was made and reason for symptoms
Discussion regarding normal blood glucose levels and targets, need for immediate insulin treatment, and its mechanism of action
Practical skills including how to draw up and administer insulin, blood glucose testing, blood and urine ketone testing
Introduction to diabetes technology
Basic dietary guidelines
Simple explanation of symptoms and management of hypoglycaemia
Diabetes at school
Importance of medical alert identification
Psychological adjustment to the diagnosis
Emergency telephone contacts

Source: Modified from Pihoker et al. 2018 [75].

Table 69.2 Continuing education curriculum.

Insulin types, actions, and adjustments based on self-monitoring of blood glucose
Monitoring and treatment goals
Discussion and initiation of diabetes technology
Mechanisms for coping with and adjusting to the diagnosis of diabetes
Nutrition, including carbohydrate counting and healthy diet for age
Management of diabetes during illness
Management of hyperglycaemia and ketosis and prevention of diabetic ketoacidosis (DKA)
Prevention, recognition, and management of hypoglycaemia
Psychosocial factors associated with diabetes, including fear of hypoglycaemia, diabetes distress, etc.
Exercise education
Travel and holiday planning
Microvascular and macrovascular complications of diabetes and their prevention
Up-to-date information on research in diabetes and new therapies and technologies in diabetes care
When age appropriate, discuss diabetes and driving, smoking, alcohol, drugs, sex and contraception, college, and employment

Source: Modified from Pihoker et al. 2018 [75].

hypoglycaemia rates [81, 82]. School-aged children will have increased understanding and involvement with their diabetes management. Providers should address school-aged children directly in addition to speaking with their parents or care providers. Education includes monitoring of blood glucose levels and injections at school, particularly during meal times, exercise, and extracurricular activities. Education should also focus on age-appropriate stepwise transition of diabetes responsibilities. This becomes particularly important in adolescence, during which there is a critical balance between promoting independent responsible management of diabetes while maintaining parental involvement.

Once treatment is established, it is common practice for children to be seen in the ambulatory setting at least every three months; visits should be more often if the child does not meet the treatment goals or intensifies treatment, for example if insulin pump treatment is initiated. During these visits, overall health and well-being are assessed, growth and vital signs are monitored, and a physical examination is performed. There should be routine screening for diabetes-associated complications and comorbidities. Blood glucose records are reviewed, including a check of HbA_{1c}, medications, and school plans. This will allow the insulin doses to be adjusted and provide a template for continued diabetes education. Age-appropriate diabetes-specific knowledge should be assessed and evaluated.

The dietitian may review dietary habits and provide ongoing nutrition education as needed. Given the rising prevalence in obesity in children and adolescents across the globe, it is recommended that age-specific healthy dietary habits are also considered in addition to the more standard carbohydrate counting review. The social worker or psychologist assesses and monitors psychosocial problems and family dynamics and the impact of diabetes care. At the conclusion of these visits, an individualized plan should be developed for each child and their family and a written copy of this plan should be provided.

The advent of new technology including downloadable glucometers, insulin pumps, and continuous glucose monitors, as well as electronic smartphone apps, has made it increasingly possible for the diabetes care team to gain insight into home management of diabetes; however, this should not replace self-monitoring and regular review of blood glucose data at home by the child and their family.

Telemedicine delivery of outpatient diabetes care

Telemedicine delivery of type 1 diabetes outpatient care has been growing in favour, especially after the Covid-19 global pandemic. Paediatric subspecialists who treat type 1 diabetes are not distributed evenly in most countries; urban areas and academic centres tend to house paediatric diabetes subspecialists, leaving other areas in the country with sparse access to specialized diabetes care. To mitigate the financial and geographical barriers to access diabetes care, telemedicine has emerged as a solution for improving access to type 1 diabetes subspecialists. While some studies have demonstrated that telemedicine and in-person visits are comparable [69], others have suggested that telemedicine results in improved type 1 diabetes-specific and psychosocial outcomes while being equally cost-effective [70, 72–74]. Telemedicine proved to be crucial during the Covid-19 global pandemic, which required a rapid transition in how diabetes care is delivered. While data are supportive that telemedicine is clinically efficacious and cost-effective [66, 68], Covid-19 galvanized paediatric diabetes providers around the world to adopt and optimize telemedicine delivery [66, 67]. Consistent with previous studies evaluating the efficacy and utility of telemedicine, emerging observational studies are supportive of telemedicine as an effective means of delivering type 1 diabetes care during the pandemic [83–85].

Given the adaptation and acceptance of telemedicine in the delivery of paediatric type 1 diabetes care, it is anticipated that the use of telemedicine will continue as an integral part of paediatric type 1 diabetes care delivery. As such, two major components necessary to the equitable and efficacious delivery of type 1 diabetes care include the ability of children and adolescents and their family to share diabetes data with their providers, and addressing the digital divide that precludes families from accessing telemedicine. The digital divide is the gap in internet, broadband, and/or devices to sustain effective telehealth that is seen between differing socioeconomic and racial or ethnic groups [86]. Type 1 diabetes management is heavily dependent on glucose and insulin data to make appropriate insulin changes. For in-person visits, data downloads are typically carried out by the multidisciplinary diabetes team; however, with telemedicine these data are to be shared by the family with the provider care team. Current methods to download and transfer diabetes data can be cumbersome and challenging. Therefore, easy transfer of clinically relevant diabetes data is an important aspect of overcoming technology and health literacy barriers in certain populations [66].

Diabetes management in school

Children with diabetes spend a significant portion of their day in school; therefore, diabetes management in school is a critical part of their diabetes management plan [87–89]. The child has the right to receive adult support for diabetes care from school personnel during school hours, outdoor school activities, and school-sponsored events away from school. Glycaemic targets should be the same in school as outside of school, but may need to be adjusted for exams or in school fitness. School personnel must be trained to provide or supervise all diabetes care prescribed by the diabetes team, be supportive of providing diabetes care, and encourage diabetes management during school hours, including:

- Insulin administration by injection or with an insulin pump.
- Testing blood glucose in young children and older, newly diagnosed children and adolescents until they are capable of performing the task independently.

• Identification and treatment for hypoglycaemia, both mild–moderate and severe.

The marked uptake in CGM use has modified the management of diabetes in the school setting. School personnel should receive education on the use of CGM, including alert notifications and trend arrows. It is also important that staff are made aware that fingerstick blood glucose values should be performed if the CGM readings appear inaccurate. In addition, the ability for parents to view glucose values and offer input to school personnel is an added benefit of CGM use in the school setting. For children using hybrid closed-loop systems, school personnel should also be informed on how to use and troubleshoot this equipment [87–89].

Children with diabetes should have a school health plan in place. The health plan should include contact information for the child's family as well as their diabetes care providers. It should also contain information regarding routine management of diabetes (blood glucose monitoring, insulin administration and dosing, snack times) and an emergency plan for management of hypoglycaemia and hyperglycaemia. Issues specific to insulin pumps include remembering to activate insulin bolus with food, disconnecting the pump during vigorous exercise or in the event of severe hypoglycaemia, pump failures, and pump alarms.

Extracurricular activities are an important component of a child's school experience and children with diabetes should be allowed to participate and have their needs accommodated accordingly. Field trips, field days, and overnight trips often require advanced planning, but a child's diabetes should never be a cause for exclusion from any school-sanctioned activity. Cognitive abilities of youths may be affected by hypo- or hyperglycaemia. Therefore, accommodations to allow for safe testing are important, including allowing the young person to check their blood glucose without penalty, the ability to treat dysglycaemia, and allowing the child to carry the equipment necessary to manage their diabetes in an easily accessible fashion [87–89].

Finally, it is important that children and adolescents and their families are aware that the diagnosis of diabetes confers legal protection where they are not excluded from the general education system; can access inclusive, quality, and free education consistent with their peers; and the educational environments should be maximized to support academic and social development [90].

Insulin treatment

The overarching goal of insulin replacement is to provide just enough insulin at an appropriate time to provide sufficient basal insulin levels as well as higher insulin levels after meals [91]. The choice of insulin regimen depends on the individual's age, duration of diabetes, dietary and activity patterns, ability to cope, and metabolic targets. Broadly, the three forms of insulin delivery include multiple daily injections (MDI), insulin pumps, and hybrid closed-loop insulin pumps. Hybrid closed-loop pumps, where sensor data are integrated in real time to inform insulin delivery and automatic modulation of basal insulin, have shown improvements in glycaemic indices and quality-of-life outcomes [92–99]. In general, insulin pump or hybrid closed-loop systems are associated with improved glycaemic outcomes when compared to MDI regimens. As noted earlier, children from low socioeconomic or racial and ethnic minority backgrounds are more likely to use MDI than insulin pumps. Providers should offer diabetes technology to all young people with diabetes and family preferences should be the drivers to initiate regimens other than MDI [100–102].

Subcutaneous insulin injection regimens

A basal bolus regimen is the preferred method for MDI regimens delivered via insulin pens or syringe and vial. Approximately 40% of the total daily dose is basal insulin analogue (e.g. glargine, detemir) and multiple doses a day with rapid-acting insulin analogue (lispro, aspart, apidra) 10–15 minutes before each meal. It is preferred that the rapid-acting insulin delivered is calculated for each meal based on the insulin sensitivity factor to correct for hyperglycaemia and carbohydrate coverage. Fixed dosing of insulin per meal is not the preferred method, as it does not appropriately match the carbohydrate intake with insulin administration, resulting in an increased risk for both hyperglycaemia and hypoglycaemia after meals. It is notable that children and adolescents from minority racial/ethnic and low socioeconomic groups are more likely to be prescribed fixed dosing despite the fact that it is suboptimal [18]. Alternate forms of teaching mealtime bolus calculations or incorporating insulin pumps may be considered in place of fixed dosing. If there is concern about inconsistent basal dose administration, insulin degludec has a longer half-life than glargine (up to 72 h vs 20–24 h, respectively) and may be considered in the regimen in place of glargine or detemir.

Historically, alternative injection regimens including intermediate-acting insulin have been used, but are not recommended due to poorer HbA_{1c} outcomes. Intermediate-acting insulins include neutral protamine Hagedorn (NPH), which is often given twice daily, and have greater inter- and intra-individual variability than the long-acting insulin analogues. These regimens include:

• Intermediate-acting human insulin twice daily and soluble human insulin 20–30 minutes prior to each meal.

• Two injections daily of a mixture of short- or rapid- and intermediate-acting insulin before breakfast and before the evening meal.

• Three injections using some variation of the following: a mixture of short- or rapid- and intermediate-acting insulin before breakfast, rapid or soluble human insulin before the afternoon snack or evening meal, and intermediate or basal/long-acting insulin before bed.

Insulin types

The pharmacokinetics of insulin analogues vary by insulin type (Figure 69.2). Basal insulin analogues include glargine, which lasts for 20–24 hours; detemir, which lasts between 6 and 23 hours and is often given as twice-daily injections (Chapter 31); and degludec, which can last up to 72 hours [104]. Common rapid-acting insulin analogues include aspart, lispro, and glulisine, which are given before a meal and to treat hyperglycaemia. Faster acting insulin aspart (Fiasp) is considered an ultra-rapid-acting insulin which has a slightly faster onset of action as well as a shorter duration of action. Regular human insulin is a short-acting insulin that has a longer onset of action and later peak of action, but is still used commonly in many places around the world. Intermediate-acting insulins, such as NPH, are often mixed with soluble human (regular) or rapid-acting analogues (aspart, lispro, or glulisine). If children are using needles and syringes in place of insulin pen devices, they and their families should be taught how to mix the insulin properly to avoid contamination. It is generally taught to draw up the clear (regular or short-acting) insulin before drawing up cloudy insulin (NPH). As per the manufacturer's instructions, glargine or detemir insulins should not be mixed with any other insulin.

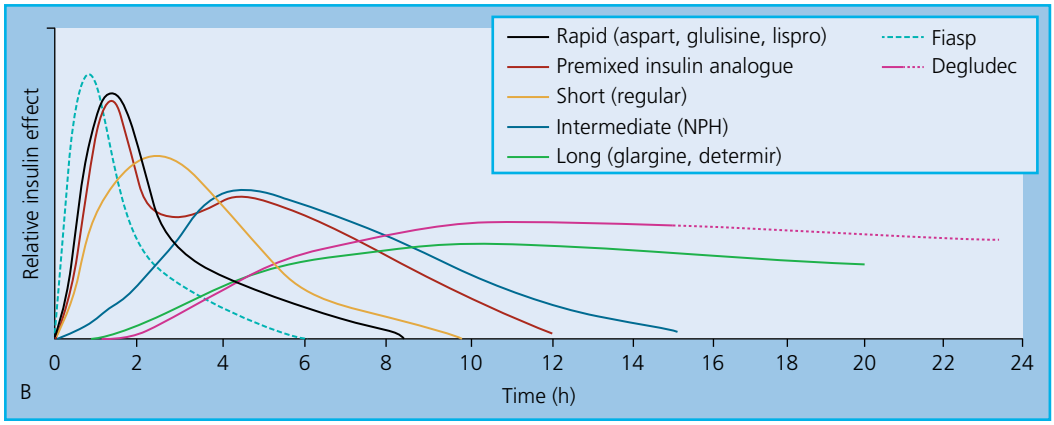

Figure 69.2 Pharmacokinetics of insulin. NPH, neutral protamine Hagedorn. Source: Data from Sperling 2020 [103].

Premixed insulins contain a mixture of regular (or rapid-acting) insulin and NPH insulin in various fixed ratios. These preparations may be useful for children who do not want to draw insulin from separate vials prior to injecting or due to cost restrictions. They may also be useful in reducing the number of injections when adherence is an issue, especially among teenagers. Premixed insulins are available for use in pen injector devices. The main disadvantage to using premixed insulin preparations is the lack of flexibility in adjusting the separate insulin doses, which is often necessary with varied food intake or during illness or exercise.

Insulin pump therapy

Insulin pump therapy is the best way to restore the body's physiological insulin profile. The pump delivers a variable programmed basal rate that corresponds to the diurnal variation in insulin needs. Prepubertal children require a higher basal rate in the early part of night, while postpubertal adolescents who experience the *dawn phenomenon* require higher rates in the morning. Two major types of insulin pumps have emerged: conventional insulin pumps (which do not incorporate CGM data) and hybrid closed-loop systems (which incorporate CGM data in real time and adjust insulin based on algorithms).

Conventional insulin pumps

The user initiates bolus doses before meals and to correct hyperglycaemia. Most pumps can receive wireless transmission of test results from glucose meters, but the child or caregiver must still manually enter the amount of carbohydrate being consumed. The pump calculates the amount of insulin needed for a meal or correction based on previously entered variables, which include insulin-to-carbohydrate ratios, insulin sensitivity factor, glycaemic target, and duration of insulin action (set at 2–8 h to estimate the duration of insulin in the body). The user may accept or override the suggestion.

Rapid-acting insulin analogues perform better in pumps than soluble human insulin, both in terms of mimicking the first-phase insulin release after meal and avoidance of post-prandial hypoglycaemia. Even with the analogues, however, insulin has to be administered at least 10–15 minutes before meals to reach effective levels to limit post-prandial glucose elevations. A longer lead time may be needed if pre-prandial blood glucose is higher than 150 mg/dl (8.3 mmol/l). Young children, picky eaters, and those with a lack of organisation may struggle with these requirements. In addition, children are often unable to predict the size of the meal. In these cases, one may administer half of the usual meal bolus in advance, with the other half, if needed, after the meal. Adherence problems include infrequent blood glucose testing, not reacting to elevated blood glucose, incorrect carbohydrate counting, or missing boluses altogether.

Children and their families must be instructed on troubleshooting and treatment of hyperglycaemia, particularly if ketones are present, as this may be an indication of a pump malfunction. If the flow of insulin becomes interrupted, ketonaemia will develop within four hours; this is particularly dangerous at night as there is no long-acting insulin on board. Syringes or insulin pens should always be available so that insulin may be administered via injection in the event of a pump failure.

Most clinical trials have demonstrated better HbA_{1c} and less severe hypoglycaemia with pump therapy, compared with MDI. Pump therapy can improve the quality of life in children who have trouble with injections or who desire greater flexibility in their lifestyle (e.g. with sleeping in, sports, or irregular eating). Insulin pumps can be particularly helpful in young children or infants who have multiple meals and snacks and require multiple small doses of rapid-acting insulin. The newer generation of insulin pumps can deliver as little as 0.025 units/h, but higher rates using diluted insulin may be needed for uninterrupted flow. Currently the most frequent complications of insulin pump treatment include failures of insulin delivery because of a displaced or obstructed infusion set, local skin infections, and DKA. Insulin pump treatment is significantly more expensive than regimens based on injections.

Hybrid closed-loop systems

Hybrid closed-loop insulin pumps integrate CGM glucose data with insulin pumps in order to modulate the basal insulin delivered in response to glucose values and glucose trends. Excepting this incorporation of glucose data to basal rates, the remaining considerations are as discussed for conventional insulin pumps, including understanding how to give mealtime boluses, troubleshooting hyperglycaemia, and recognizing pump site failures. At present, two hybrid closed-loop systems are US Food and Drug Administration (FDA) approved and more are expected in the future. The benefits of hybrid closed-loop systems include benefits of basal modifications to increase time in range and improve HbA_{1c} [92–99]. In addition, the use of hybrid closed-loop systems is associated with improvements in quality of life and psychosocial outcomes. As more hybrid closed-loop systems are approved, the uptake and use of these system are expected to increase. Consistent with disparities seen in diabetes technology use at large, there exists concern that disparities in hybrid closed-loop systems are also emerging by race or ethnicity and socioeconomic status.

Future of insulin pumps

Fully closed-loop systems, allowing the insulin pump to be directed automatically by a CGM with minimal human input, are being tested. The goal of a closed-loop or automated insulin delivery is to allow for minimal input from the young person or parent to maintain target glucose levels. There is a particular interest in the automated system accounting for unannounced boluses in a fashion that maintains euglycaemia. Dual-hormone systems that include both glucagon and insulin in the regulation of glucose levels are being studied [105].

Nutrition

Nutritional management in children with diabetes remains a key component of diabetes care and education; a paediatric dietitian should be part of the diabetes care team. Carbohydrate counting is the foundation of nutrition education in type 1 diabetes in order to approximate insulin boluses. In addition, a key strategy should be prevention of overweight and obesity. The management does not require a restrictive diet, just a healthy dietary regimen from which the children and their families can benefit. Current guidelines target optimal glycaemic indices, reduction of cardiovascular risk, psychosocial well-being, and family dynamics [89, 106]. A thorough dietary history should be obtained, including the family's dietary habits and traditions, the child's typical meal times, and patterns of food intake. Weight loss or poor weight gain may be a sign of illness (such as infection, coeliac disease, or hyperthyroidism), insulin omission, or disordered eating [89, 106, 107].

Insulin pump and MDI therapy utilize carbohydrate counting in which the grams of carbohydrate to be eaten are counted and a matching dose of insulin is administered. This plan allows for the greatest freedom and flexibility in food choices, but it requires expert education and commitment and may not be suitable for many families or situations (e.g. school lunches, teenagers). Books and apps are now available to help calculate carbohydrate intake more accurately. Less preferred methods of accounting for carbohydrates include carbohydrate exchanges or consistent carbohydrate meal plans, as they are less flexible. Exchange planning teaches that it is not necessary to count precise grams. Exchanges are taught as either 10 or 15 g servings of carbohydrate. The exchange plan can enable a more consistent daily intake of carbohydrate. The constant carbohydrate meal plan was used often in the past with insulin regimens based on NPH and regular insulin, where carbohydrate intake and the amount of insulin were kept relatively constant from day to day. It has been perceived as too restrictive and a potential source of conflict.

The concept of the glycaemic index has been shown to provide additional benefit to glycaemic management (Chapter 27). Low glycaemic index carbohydrate foods, such as wholegrain breads, pasta, temperate fruits, and dairy products, may lower post-prandial hyperglycaemia. A glycaemic load approach to predicting the post-prandial blood glucose response, based on the glycaemic index of the food and the portion size, has not been fully explored in children. With the rising rates of obesity, dietary changes to combat obesity and insulin resistance are of greater interest. However, data are limited on the impact of diets on glycaemic indices and weight management in the young person with type 1 diabetes. For example, while low-carbohydrate diets have been effective in weight management for adults with diabetes, concern exists about the impact on growth and development and they are not currently recommended in children with diabetes [108, 109]. Helpful principles foundational to a healthy diet for children with diabetes are shown in Table 69.3.

Table 69.3 Principles of dietary planning in children with diabetes.

- Eat a well-balanced diet, with daily energy intake distributed as follows:
  - Carbohydrate 45–55% (sucrose intake up to 10% total energy)
  - Fat 30–35% (<10% saturated fat + trans fatty acids)
  - Protein 15–20%
- Importance of routine mealtimes with limitations on snacking
  - Incorporate healthy snacks if necessary to maintain a healthy weight or prevent binge eating
- Use snacks to prevent and treat hypoglycaemia, but avoid overtreatment
  - Snacks should be used in moderation to avoid excess calorie intake
  - Most children will have a mid or late afternoon snack
  - Modern insulin regimens reduce the need for daytime and bedtime snacks required by traditional insulin profiles
- Gauge energy intake to maintain appropriate and healthy weight and body mass index
  - Overinsulinization, *forced* snacking, and excess food intake to prevent or treat hypoglycaemia promote excessive weight gain and should be avoided
  - Eating disorders are common in teenagers with diabetes, particularly girls
- Recommended fibre intake for children older than 1 year: 3.3 g/MJ; children older than 2 years should eat (age in years + 5) g/d fibre
- Avoid foods high in sodium that may increase the risk of hypertension; target salt intake to less than 4 g/d (sodium chloride)
- Avoid excessive protein intake (athletes should not require protein supplements)
- Protein requirements after infancy are approximately 1 mg/kg/d and 0.9 mg/g/d in adolescence
- Excessive carbohydrate restriction are not recommended for children and adolescents with type 1 diabetes due to deleterious effects on growth, increased cardiovascular disease, and the risk of disordered eating behaviours
- Children with diabetes have the same vitamin and mineral requirements as other healthy children; however, hypovitaminosis D is common and screening and supplementation are recommended
- There is no evidence of harm from an intake of artificial sweeteners in doses not exceeding acceptable daily intakes
- Specially labelled diabetic foods are not recommended because they are not necessary, are expensive, are often high in fat, and may contain sweeteners with laxative effects. These include the sugar alcohols such as sorbitol
- While alcohol intake is generally prohibited in adolescents, teenagers continue to experiment with and sometimes abuse alcohol. Alcohol may induce prolonged hypoglycaemia in young people with diabetes (up to 16 h after drinking)
- Carbohydrate should be eaten before, during, and/or after alcohol intake. It may also be necessary to lower the insulin dose, particularly if exercise is performed during or after drinking (e.g. dancing)

Exercise

Children with diabetes derive the same health and leisure benefits from exercise as children without diabetes and they should be allowed to participate with equal opportunities and equal safety [106]. Current guidelines recommend 60 minutes of moderate to vigorous activity for youths with type 1 diabetes, yet most children do not meet these guidelines [106]. Numerous barriers exist with regard to the dual management of type 1 diabetes and exercise, such as fear of hypoglycaemia and dysglycaemia [110–112].

Physiologically, during exercise in children without diabetes there is a decrease in pancreatic insulin secretion and an increase in

counter-regulatory hormones, resulting in an increase in liver glucose production (Chapter 28). This matches skeletal muscle uptake of glucose during exercise, maintaining stable blood glucose concentrations under most conditions. In children with type 1 diabetes, there is no pancreatic regulation of insulin in response to exercise and there may be impaired counter-regulation. These factors combine to increase the risk of hypoglycaemia and hyperglycaemia during exercise. It is helpful to keep an exercise record noting the most recent insulin dose, timing and type of exercise, blood glucose levels before and after exercise, snacks eaten, and the time of any episode of hypoglycaemia. Factors affecting the glycaemic response to exercise include exercise duration, exercise type, timing and intensity of activity, overall metabolic and glucose management, type and timing of insulin injections and its absorption, type and timing of food, muscle mass and conditioning, and degree of stress or competition [26, 106].

Preventing hypoglycaemia

There are numerous strategies to prevent exercise-related hypoglycaemia, such as order of exercise intensity, insulin adjustments, and carbohydrate intake. Blood glucose levels should be checked before, during, and after the exercise. Target glucose level before the start of exercise is >5 mmol/l or >90 mg/dl. If glucose levels are below target, it is recommended to ingest 10–20 g of carbohydrates and delay exercise until glucose values are in target [106, 107, 113].

Timing of exercise type

The timing of exercise intensity (aerobic vs anaerobic) can be one strategy to optimize glycaemic levels during exercise (Figure 69.3) [106]. Anaerobic exercises, such as short sprints or weight lifting, are associated with a rise in glucose values during exercise followed by delayed hypoglycaemia. In contrast, aerobic exercise, such as cycling or long-distance running, results in lowered glucose values both during and after exercise. The blood glucose prior to exercise initiation can inform the order of exercise type. For example, if the blood glucose value prior to exercise initiation is above target, youths can start with aerobic exercise followed by anaerobic. If blood glucose values are in target at the start of exercise, resistance or anaerobic exercise followed by aerobic exercise is thought to optimize glucose stability during exercise.

Insulin modification

Another strategy to combat exercise-related hypoglycaemia is insulin dose modification. Reduction of basal insulin 45–90 minutes in advance of activity informed by exercise duration and intensity can be achieved in those using insulin pumps [113]. For example, 30 minutes of mild aerobic exercise can be accompanied by a 25% basal reduction, whereas heavy aerobic exercise would warrant a 75% basal reduction. In contrast, 30 minutes of intense anaerobic exercise does not warrant a pre-exercise decrease in basal insulin [113]. For those who do not use insulin pumps, the long-acting insulin should be reduced the evening before a day of intense physical activity [106, 107]. A 25–50% reduction of mealtime boluses before or after exercise can also be incorporated to prevent exercise-related hypoglycaemia. For exercise anticipated within the first hour after eating, the dose of rapid-acting insulin before the meal may need to be decreased by 25–75% (depending on the intensity of the exercise). For evening exercise, reduction of the evening meal

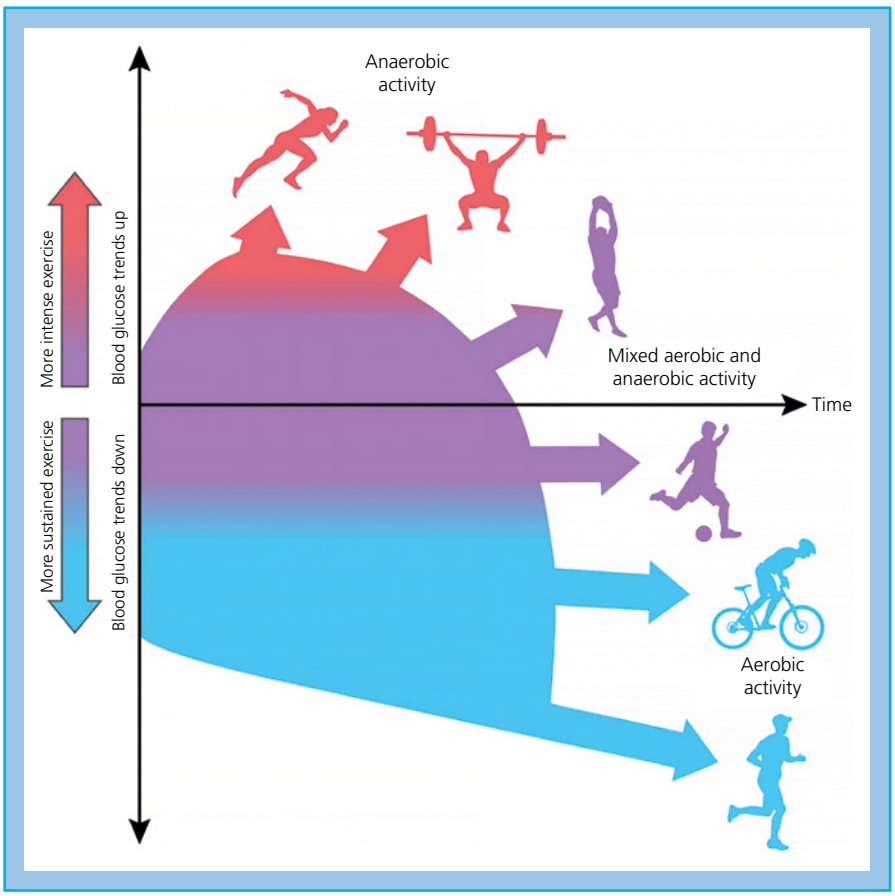

Figure 69.3 Impact of glucose trends by exercise intensity type. Source: Reproduced by permission from Adolfsson et al. 2018 [106].

rapid-acting insulin by 25–75% as well as ingesting 10–15 g of fast-acting carbohydrate before the activity can help avoid hypoglycaemia [106, 113]. If the young person needs to disconnect from the pump in order participate in an activity, they can do one of the following:

- Bolus part of the basal insulin missed prior to exercise (particularly if the pre-exercise blood glucose level is elevated) and the remainder administered after exercise.
- Bolus half of the insulin missed while disconnected after exercise.
- Bolus all of the insulin missed while disconnected after exercise.

In general, the pump should not be disconnected for longer than two hours. If necessary, the pump should be reconnected briefly and a bolus administered prior to disconnecting again. New technologies with low glucose suspend may help with decreasing risk of hypoglycaemia during and after activity. Reduction of insulin in contrast to ingestion of carbohydrates to prevent hypoglycaemia has added benefit for weight.

The site of insulin injection should also be taken into account. Exercise increases blood flow in the part of the body being used, increasing insulin absorption if that area is where the insulin injection was administered. For example, the insulin dose should not be administered in the legs prior to running.

Carbohydrate intake Carbohydrate consumption prior to, during, and after exercise can be utilized to avoid and treat hypoglycaemia. In order to avoid unnecessary carbohydrate and calorie intake, which is associated with obesity and weight gain, insulin modification and timing of exercise intensity are more effective for weight management. For short-duration activity, sports drinks with simple sugars provide optimal absorption and usually prevent hypoglycaemia for the next 30–60 minutes. For activity of longer duration, solid foods containing carbohydrates that are digested more slowly should be consumed in addition to a liquid with simple sugars. Extra snacks should always be available to the child during exercise.

The child's coaches and teammates or other responsible adults and peers should be aware of the signs and symptoms of hypoglycaemia.

Delayed hypoglycaemia

Hypoglycaemia can occur up to 24 hours after exercise secondary to increased glucose transport into the skeletal muscle, the late effect of increased insulin sensitivity, and the delay in replenishing liver and muscle glycogen stores. Blood glucose levels must be monitored for several hours following exercise, at bedtime, and sometimes during the night on days with strenuous exercise. Utilization of CGM with exercise allows for prediction of blood glucose with trend arrows and detection of hypoglycaemia during and after exercise without finger-stick blood glucose checks. Consider a longer-lasting snack (containing a solid carbohydrate, protein, and fat) at bedtime and reducing the insulin dose, as discussed earlier.

Ketones and exercise

In situations of insufficient insulin intake or increased insulin resistance, whether it be from poor glycaemic management or from illness, exercise may be dangerous because of the effect of uninhibited action of the counter-regulatory hormones. Children with diabetes should not participate in strenuous exercise if the pre-exercise blood glucose level is high (>250 mg/dl, >14 mmol/l) and urine ketones (small or more) or blood ketones (≥0.5 mmol/l) are present. Treat ketones and postpone exercise until ketones have cleared (Figure 69.4) [106].

Hypoglycaemia

Hypoglycaemia is the most common acute complication in the treatment of type 1 diabetes and severe hypoglycaemia is responsible for a significant proportion of deaths in people with diabetes

B-ketones / B-glucose	B-glucose ≤14 mmol/l (≤252 mg/dl)	B-glucose >14 mmol/l (>252 mg/dl)	B-glucose
B-ketones ≥1.5 mmol/l	Add carbohydrates + insulin and give ½ correction dose of insulin with pen or syringe Act according to plan	Give ½ correction dose of insulin with pen or syringe Act according to plan	Avoid exercise
B-ketones 1.1–1.4 mmol/l	Add carbohydrates + insulin and give ½ correction dose of insulin with pen or syringe	Give ½ correction dose of insulin with pen syringe	Wait 60 min after correction and ensure decreasing glucose value Then OK to exercise
B-ketones 0.6–1.0 mmol/l	Add carbohydrates + insulin and give ½ correction dose of insulin with pen or syringe	Give ½ correction dose of insulin with pen or syringe	Wait 15 min after correction Then OK to exercise
B-ketones <0.6 mmol/l	No signs of DKA	No signs of DKA	Exercise is OK

Figure 69.4 Glucose, ketone, and exercise considerations. B-glucose, blood glucose; B-ketones, blood ketones; DKA, diabetic ketoacidosis.
Source: Reproduced by permission from Adolfsson et al. 2018 [106].

aged <40 years (Chapter 40) [114]. According to the most recent guidelines published by ISPAD, hypoglycaemic events can be thought of in three tiers. At the least severe, it recommends a clinical hypoglycaemia alert threshold at 70 mg/dl (3.9 mmol/l). Treatment should be initiated at this level due to the risk of a further drop in blood glucose level. A level below 54 mg/dl (3.0 mmol/l) is considered clinically important or serious hypoglycaemia; at this level children may experience a defective response by counter-regulatory hormones as well as impaired awareness. Rather than by a specific blood glucose threshold, severe hypoglycaemia is defined by the presence of significant cognitive impairment requiring assistance from another person to administer oral glucose, glucagon, or other intervention [79, 114]. Severe hypoglycaemia occurs in approximately 6% of persons with diabetes, although less severe hypoglycaemia occurs much more frequently [115]. The largest risk factors for severe hypoglycaemia are lower socioeconomic status and race, while younger age, longer diabetes duration, lack of private health insurance, and multiple daily injections also increase the risk [115].

While lower HbA_{1c} has historically been considered a risk factor for hypoglycaemia, continuing improvements in diabetes technology, including CGM, insulin pumps, and hybrid closed-loop systems, have made it increasingly possible to maintain an appropriately intensive insulin treatment and target HbA_{1c} without significantly increasing hypoglycaemic events [97, 116–118]. Longitudinal studies in Australia and Germany showed a simultaneous decrease in both average HbA_{1c} and severe hypoglycaemic events over a 20-year period [119]. Use of CGM and automated insulin delivery systems with predicted low glucose suspend reduce time spent in hypoglycaemia [78, 98].

Signs and symptoms

Signs and symptoms of hypoglycaemia are as follows:

- *Autonomic signs and symptoms*: shakiness, palpitations, sweatiness, pallor.
- *Neuroglycopaenic signs and symptoms*: difficulty concentrating, blurred or double vision, disturbed colour vision, difficulty hearing, slurred speech, poor judgement and confusion, problems with short-term memory, dizziness and unsteady gait, loss of consciousness, seizure, death.
- *Behavioural signs and symptoms*: irritability, erratic behaviour, nightmares, inconsolable crying.
- *Non-specific symptoms*: hunger, headache, nausea, tiredness.

Early warning signs and symptoms of hypoglycaemia are much more difficult to identify in young children.

Treatment

In mild or moderate symptomatic hypoglycaemia, after documenting a blood glucose of ≤70 mg/dl (3.9 mmol/l):

- Provide immediate oral, rapidly absorbed 5–15 g glucose or sucrose: glucose tablets, Smarties, or 100 ml of a sweet drink (juice, soda).
- Retest blood glucose in 10–15 minutes. If no response or inadequate response, repeat as above.
- As symptoms improve and euglycaemia is restored, ingest a solid snack or a meal (e.g. fruit, bread, cereal) to prevent recurrence.
- Retest blood glucose in 20–30 minutes to confirm that target glucose has been maintained.

In severe hypoglycaemia, where the child has an altered mental status and is unable to assist in their care, may be unconscious, and/or is seizing, urgent treatment with parenteral glucagon or dextrose is required.

Glucagon

Rescue glucagon is given intranasally, intramuscularly, or subcutaneously (10–30 μg/kg body weight):

- 0.5 mg for those <12 years.
- 1 mg for those >12 years or >45 kg.

Traditional formulations of glucagon were not stable in solution and thus required that the caregiver mix glucagon powder with saline prior to injection. Recently, both premixed glucagon injection pens as well as intranasal glucagon [120] have become available in the USA, making emergency administration more accessible for the average caregiver. Glucagon administration may be repeated in 5–10 minutes if the response was inadequate; however, it is likely to be ineffective after prolonged fasting. Side effects include vomiting and tachycardia.

Mini-dose glucagon

As an alternate to a full rescue dose of glucagon, typically used in settings of severe hypoglycaemia, mini-dose glucagon also has utility in some clinical scenarios. Mini-dose glucagon has the largest utility in achieving euglycaemia in the setting of mild or impending hypoglycaemia, typically in the setting of a concurrent illness (nausea, vomiting, diarrhoea) or inadequate oral carbohydrate intake or absorption [121, 122]. In such settings, mini-dose glucagon should be given as a subcutaneous injection with an insulin syringe, and can be repeated every 2–4 hours. It is estimated that 1 unit on the insulin syringe is equal to approximately 10 μg of glucagon and individuals are dosed 1 unit/year of age, with a maximum of 15 units (~150 μg) and a minimum of 2 units (~20 μg) in children <2 years of age.

Dextrose

Dextrose can be given intravenously by trained medical staff if glucagon is unavailable or recovery is inadequate in a hospital setting or by paramedics:

- Intravenous dextrose should be administered slowly over several minutes (e.g. dextrose 10% at 2–3 ml/kg).
- Rapid administration or higher concentration may result in an excessive rate of osmotic change, phlebitis, and extensive tissue damage, if extravasated.

Close observation and monitoring of blood glucose are essential because vomiting is common in response to glucagon and hypoglycaemia may recur. Severe headache and transient paresis lasting up to 24 hours are not uncommon, but generally do not require radiological work-up.

Hypoglycaemia unawareness

Hypoglycaemia unawareness occurs when there is reduced awareness of the onset of hypoglycaemia, typically due to a blunted response of counter-regulatory hormones in the setting of recurrent hypoglycaemic events. A single hypoglycaemic episode can lead to hypoglycaemia unawareness secondary to a decrease in counter-regulatory responses, but it is usually seen in children who have multiple periods of blood glucose <70 mg/dl (3.9 mmol/l). Avoiding subsequent hypoglycaemia for 2–3 weeks may reverse this loss of awareness, although these changes can persist for months or years in some individuals [123].

Prevention

Hypoglycaemia occurs more frequently:

- When the treatment regimen or lifestyle is altered (increased insulin, less food, more exercise).
- In younger children.
- With lower HbA_{1c} levels.

- With previous severe hypoglycaemia.
- When there is hypoglycaemia unawareness.
- During sleep.
- After alcohol ingestion.

Children and families should be aware of these risk factors so that glucose monitoring and insulin regimens can be changed accordingly. There is an increased risk for hypoglycaemia during, immediately after, and up to 24 hours after exercise. Untreated coeliac disease and hypoadrenalism (Addison disease) may also increase the risk of hypoglycaemia, and should be screened for in individuals with recurrent, severe, or unexplained hypoglycaemia.

Nocturnal hypoglycaemia is often asymptomatic and should be suspected if the morning blood glucose is low and/or there are episodes of confusion, nightmares, or seizures during the night, or if there is impaired thinking, altered mood, or headaches on awakening. Nocturnal hypoglycaemia can be confirmed with blood glucose monitoring during the night and may be prevented by including more protein and fat in the bedtime snack. Care should be taken that this does not occur at the expense of high overnight blood glucose levels.

There is an association between hypoglycaemia and decrease in cognitive functioning in children with type 1 diabetes, particularly in children diagnosed before the age of 5–6 years. Recurrent severe hypoglycaemia has been associated with worsened long-term memory, attention, and verbal IQ, but studies have been inconsistent. Severe hypoglycaemia can increase worry for the parent and the person with diabetes, and lead to poor sleep, emergency room visits, hospitalizations, excessive lowering of insulin doses, and subsequent worsening of glycaemic measurements. Long-term follow-up of the Diabetes Control and Complications Trial (DCCT) participants has been reassuring that there was no evidence for permanent neurocognitive changes related to hypoglycaemia in adolescents and young adults, suggesting that the effect of severe hypoglycaemia on long-term neuropsychological functioning may be age dependent [124]. Conversely, hyperglycaemia causes changes in functional magnetic resonance imaging (fMRI) and neurological testing, further underlining the importance of optimizing time spent in euglycaemia [125, 126].

Ultimately, hypoglycaemia is frequently predictable and should be prevented. Children and their caregivers must be taught to recognize the symptoms of hypoglycaemia and treat them immediately and appropriately. Children with diabetes should always carry around a source of rapid-acting glucose and should wear identification noting that they have diabetes. The diabetes care provider should be notified if a child is having recurrent episodes of symptomatic hypoglycaemia or if there is hypoglycaemia unawareness. This will facilitate discussions to adjust insulin regimens, food intake patterns, blood glucose goals, and monitoring. CGM helps detect and avoid hypoglycaemia and the use of hybrid closed-loop insulin pumps with predicted low glucose suspend can also prevent hypoglycaemia by decreasing insulin infusion rates based on the rate and degree of blood glucose decreases [93–96, 98].

Sick-day management

Children with diabetes in good metabolic measures should not experience more illness or infections than children without diabetes; however, they will go through their share of routine infections, which can be challenging for their caregivers. In addition to routine childhood immunizations, influenza, meningococcal, and pneumonia vaccines are recommended for all children with diabetes. When children with diabetes become ill, the underlying precipitating illness should be treated promptly.

Healthcare providers should equip families soon after diagnosis with the tools necessary to avoid dehydration, uncontrolled hyperglycaemia or ketoacidosis, and hypoglycaemia. Face-to-face education and written instructions are important, but most parents require telephone advice when first facing sickness in their child and some may need repeated support. Over time, most parents should be able to manage sick days independently as well as identify appropriate times to seek help from their diabetes provider or emergency services. Children and their families should immediately seek medical attention if:

- Blood glucose concentrations continue to rise despite extra insulin.
- Blood glucose concentrations remain persistently below 70 mg/dl (3.5 mmol/l).
- Blood ketones are higher than 1.5 mmol/l or ketonuria is severe and persistent.
- The child becomes exhausted, confused, dehydrated, or develops difficulty in breathing, severe abdominal pain, or a severe hypoglycaemic reaction.

Missed insulin injection, inactivated insulin, or interruption of insulin delivery from pump may lead to sick days as well, especially in older children. While treatment is essentially the same as for hyperglycaemia in the course of an infection, the differential diagnosis is important for prevention of recurrent events.

Hyperglycaemia is seen in many illnesses, particularly those associated with fever, as a result of elevated levels of stress hormones, which promote gluconeogenesis and insulin resistance. Severe illness increases ketone body production secondary to inadequate insulin action or insufficient oral intake of carbohydrates. By contrast, illnesses associated with vomiting and diarrhoea can lead to hypoglycaemia secondary to decreased food intake, poor absorption, and slower gastric emptying.

In general, during illness, blood glucose concentrations must be monitored more frequently – at least every 3–4 hours and more often when blood glucose concentrations are outside the target range (e.g. 80–200 mg/dl; 4.4–11.1 mmol/l). Urinary or blood ketones must be checked at least twice daily and more often if previously elevated or when blood glucose concentration exceeds 300 mg/dl (17.6 mmol/l). When available, blood ketones (β-hydroxybutyrate, using e.g. a Precision Xtra®/Xceed Pro® meter, Abbott Laboratories, Chicago, IL, USA) can provide more specific and timely assessment of ketosis compared to urine ketone testing:

- The presence of ketones when blood glucose concentrations are persistently elevated above 200 mg/dl (11.1 mmol/l) indicates the need for supplemental insulin and fluids.
- The presence of ketones when blood glucose concentrations are low or normal, especially during gastrointestinal illness, indicates insufficient oral intake of carbohydrates (starvation ketones). In this case, ketones do not reflect insulin deficiency, but rather a physiological response and may protect the child from severe hypoglycaemia, as β-hydroxybutyrate is the only alternative fuel to glucose for the brain. Supplemental insulin is contraindicated as it will likely cause hypoglycaemia; the correct treatment includes fluids with glucose.

Insulin therapy must never be stopped during a sick day, although the dose may need to be decreased if the child is vomiting or eating less than usual. A fasting child still requires approximately 40% of the usual daily insulin dose, as long-acting basal insulin, to cover

basic metabolic needs and prevent ketoacidosis; however, infections associated with normal food intake often require an increase of basal insulin by 10–15%. In addition, extra doses of rapid-acting insulin are usually needed to correct hyperglycaemia, prevent ketoacidosis, and avoid hospital admission. These doses may be repeated every 2–4 hours as needed based on the results of blood glucose and ketone monitoring.

An example of a typical management approach when ketonuria/ketonemia and blood glucose concentrations are greater than 200 mg/dl (11.1 mmol/l) includes:

- Usual high blood glucose correction, e.g. 1 unit of rapid-acting insulin for each 50 mg/dl (2.8 mmol/l) above 100 mg/dl (5.5 mmol/l), if blood ketones <0.6 mmol/l or urine ketones negative/small.
- Injection of rapid-acting insulin at 10% of the total daily dose, if blood ketones 0.6–1.5 mmol/l or urine ketones moderate or large.
- Injection of rapid-acting insulin at 10–20% of the total daily dose if blood ketones >1.5 mmol/l or urine ketones moderate or large.
- As acidosis is present in most children with hyperglycaemia and blood ketones >3.0 mmol/l, this warrants referral to an emergency department.

Children using insulin pumps who develop hyperglycaemia and moderate or large urine ketones (or ≥1.0 mmol/l blood ketones) must always consider the possibility of an interruption in insulin delivery. If blood glucose levels do not decrease appropriately after an insulin bolus from the pump, the correction bolus of short-acting insulin should be given as an injection and the pump infusion set should be changed. A temporary increase in the basal rate by 20% or more may be required until blood glucose concentrations begin to normalize and ketones clear.

If hypoglycaemia <70 mg/dl (<3.9 mmol/l) persists and the child is unable to tolerate any oral intake, an injection of mini-dose glucagon may reverse the hypoglycaemia and enable oral fluid intake to resume. This dose of glucagon is not to be used for the emergency treatment of severe hypoglycaemia.

Hydration status must be followed closely. Fever, hyperglycaemia with osmotic diuresis, and ketonuria all increase fluid losses. Households should maintain a supply of sugar and electrolyte-containing fluids:

- Oral water is sufficient to prevent dehydration in uncomplicated cases of hyperglycaemia.
- If there is an ongoing fluid loss from diarrhoea or vomiting, hydration liquids should contain salt in addition to water (e.g. Pedialyte®, Abbott Laboratories). These preparations contain 25–30 g/l glucose, 45–90 mEq/l sodium, 30 mEq/l bicarbonate, and 20–25 mEq/l potassium. Oral rehydration fluid can be made at home by mixing half of a flat teaspoon of salt (~3 g NaCl = ~50 mEq sodium), seven teaspoons of sugar (28 g), and (optionally) 100 ml of orange juice into 1 l water.
- If there is difficulty eating or keeping food down and the blood glucose is falling below 200 mg/dl (11.1 mmol/l), sports drinks should be administered. They contain fewer electrolytes but higher amounts of glucose (e.g. Gatorade® [PepsiCo., Purchase, NY, USA] contains 255 g/l glucose, 20 mEq/l sodium, 3 mEq/l bicarbonate, and 3 mEq/l potassium).
- If the blood glucose is falling below 100 mg/dl (5.6 mmol/l), fluids with a higher concentration of sugar are recommended (e.g. juice or non-carbonated regular soda containing approximately 70 g glucose per 100 ml). These fluids contain almost no sodium and are not appropriate in large amounts for children with diarrhoea.

The required volume of oral fluid replacement is the sum of maintenance volume, deficit, and ongoing losses. In practical terms, infants and toddlers with diabetes who have vomited more than twice or have multiple loose stools may need to be referred to an emergency department for evaluation and intravenous fluids. Those with milder symptoms can be given oral fluid therapy at home using small amounts (5 ml) of cold fluids every 5 minutes. Most children with vomiting can be successfully orally rehydrated with persistent gentle encouragement by the parents.

Use of antiemetic medication at home should be approached cautiously, especially in young children, as it may mask acute abdominal processes such as appendicitis, volvulus, or intussusception and may have significant adverse effects. Where appropriate, ondansetron can be used to contain vomiting in children who have been properly evaluated by a physician and selected older children presenting without abdominal pain.

Monitoring and goals of diabetes management

HbA_{1c} is the only measure of mid- to long-term glycaemic levels for which robust outcome data are available (Chapter 29). Elevated HbA_{1c} predicts long-term microvascular and macrovascular complications, but has its limitations. In the DCCT, an HbA_{1c} of 53 mmol/mol (7.0%) corresponded to a higher average blood glucose concentration (measured seven times a day) of 192 mg/dl (10.7 mmol/l) in the conventionally treated participants compared with 163 mg/dl (9.1 mmol/l) in those in the intensively treated group. Consequently, the same HbA_{1c} level conferred a significantly higher risk of microvascular complications and hypoglycaemia in the conventionally treated group compared with the intensively treated group. HbA_{1c} is only one of the measures of optimal glycaemic management, with other measures including documented hypoglycaemia, type of treatment, the person's age, and quality of life. Ideally, there should be 4–6 measurements/year in younger children and 3–4 measurements/year in older children.

Self-monitoring of blood glucose (SMBG) provides immediate and daily documentation of hyperglycaemia and hypoglycaemia, helps to determine immediate and daily insulin requirements, detects hypoglycaemia, and assists in its management. Blood glucose is best measured during the night, after the overnight fast, before meals, and two hours after a meal – typically 4–6 times a day. Blood glucose should also be measured in association with illness, exercise, and prior to driving a car. The frequency of SMBG is associated with improved HbA_{1c} in people with type 1 diabetes. Even with CGM, SMBG remains an important part of diabetes care.

Targets for HbA_{1c} and SMBG proposed by ISPAD [127] and the American Diabetes Association (ADA) [128] are summarized in Table 69.4.

Continuous glucose monitoring metrics

While HbA_{1c} has long been the gold standard marker of glycaemic management, there are limitations to HbA_{1c}, namely the inability to evaluate glycaemic excursions in real time and to measure glycaemic variability. While the correlation between SMBG and HbA_{1c} is established, an HbA_{1c} of 7.0% can have wide variability in mean glucose values [129]. In addition, variations in HbA_{1c} are reported by race and ethnicity. For these reasons, the time-in-range data offered by CGM are increasingly being used and are emerging as a very valuable tool in evaluating glycaemia.

Table 69.4 Biochemical targets of glycaemic management.

	Targets
HbA_{1c}	
DCCT standardized (%)[a]	<7.0%
IFCC (mmol/mol)	<58 mmol/mol
CGM	
Time in range	>70%
Hypoglycaemia	<4%
SMBG, mmol/l (mg/dl)	
Fasting or pre-prandial blood glucose	4–8 (70–145)
Post-prandial blood glucose	5–10 (90–180)
Bedtime blood glucose	6.7–10 (120–180)
Nocturnal blood glucose	4.5–9 (80–162)

These targets are intended as guidelines; each child should have their targets individually determined.
[a] The DCCT conventional adult cohort had a mean HbA_{1c} value of 8.9% (74 mmol/mol). Both DCCT and Epidemiology of Diabetes Interventions and Complications (EDIC) have shown poor outcomes with this level.
CGM, continuous glucose monitoring; DCCT, Diabetes Control and Complications Trial; HbA_{1c}, glycated haemoglobin; IFCC, International Federation of Clinical Chemistry; SMBG, self-monitoring of blood glucose.

CGM devices can be categorized into three general types: real-time CGM, intermittently scanned CGM, and professional CGM. Real-time CGM systems measure and display glucose levels continuously, whereas intermittently scanned CGM systems measure glucose levels continuously, but only display values when accessed by a reader. Professional CGM systems, unlike real-time or intermittently scanned systems, are not owned by the individual and are devices that are placed in the provider's office and worn for a discrete period of time to assess glycaemic patterns and trends [128, 130]. The goal time in range (70–180 mg/dl; 3.9–10.0 mmol/l) is >70% and <4% time in hypoglycaemia (<70 mg/dl; <3.9 mmol/l) [114]. CGM targets are presented in Figure 69.5 [128]. An increase in time in range by 5% is associated with clinically significant benefit in diabetes outcomes [131, 132].

CGM is now becoming the gold standard for glucose management and is associated with improvements in diabetes-related outcomes [128, 130]. Specifically, improvements are seen in HbA_{1c} irrespective of type of insulin delivery (MDI or insulin pump) as well as a decrease in both hyper- and hypoglycaemia. In the last decade, with improvements in CGM technology including better accuracy and ease of use, CGM use has increased across the globe. However, although CGM use has increased in more-resourced countries, emerging data demonstrate disparities in CGM uptake: youths from low socioeconomic and racial and ethnic minority groups have the lowest CGM use [17, 133]. CGM uptake is lower in less-resourced countries. In these countries, meeting SMBG guidelines of ≥5 checks/day is challenging due to the limited availability of diabetes devices. For resource-limited countries, a tiered level of care to work towards establishing guidelines-based care has been published [134].

Psychological care

Psychosocial and behavioural factors play an important role in the management and outcomes of type 1 diabetes. Children and adolescents with type 1 diabetes are more frequently diagnosed with and treated for psychiatric disorders, disordered eating, and neurocognitive problems than the general population [107, 135]. In addition, many young people and their families face an increase in general and diabetes-specific stress due to the demanding nature of

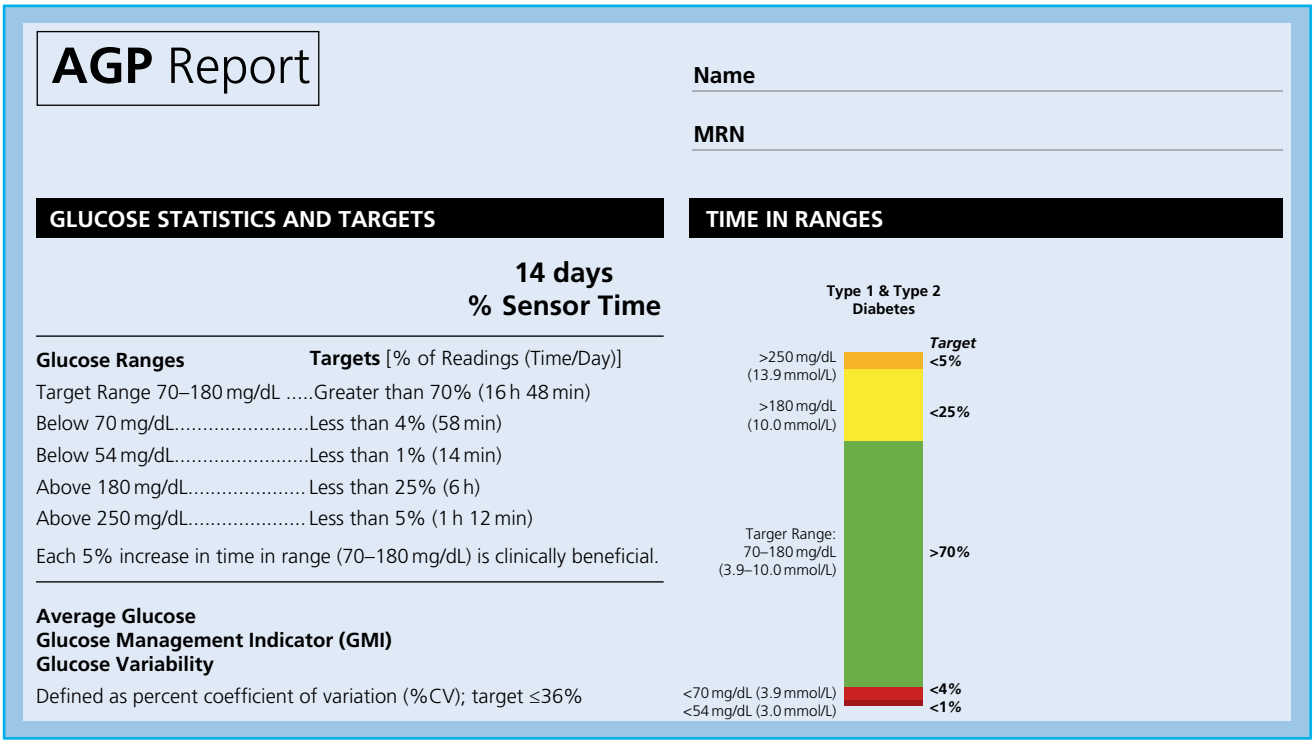

Figure 69.5 The ambulatory glucose profile and target time in range. Source: Reproduced by permission from American Diabetes Association 2020 [128].

type 1 diabetes management. The diagnosis of type 1 diabetes changes the lives of affected families and can pose lifelong challenges. Children with type 1 diabetes are at risk for adjustment disorder during the initial period after diagnosis (Chapter 63). For these reasons, routine and consistent psychosocial screening is recommended for all young people with type 1 diabetes to evaluate for symptoms of depression, diabetes distress, disordered eating, parental distress, and other psychosocial factors [107, 135]. In consort with standardized screening, an interdisciplinary diabetes health team, inclusive of mental health providers, should maintain regular contact with youths and their families.

Diabetes providers should be aware of diabetes-specific psychosocial concerns that can affect young people and their families, in addition to general mental health disorders such as depression and anxiety. Diabetes distress is defined as the emotional burden and worries that are inherent to the diagnosis and management of diabetes. Diabetes distress is common and persistent throughout the lifetime of an individual with type 1 diabetes and has adverse impacts on both HbA_{1c} and quality of life [136–138]. Addressing diabetes distress in addition to symptoms of depression, anxiety, and other mental health disorders is associated with an improvement in HbA_{1c} and quality-of-life measures [139–141]. Addressing psychosocial factors is also associated with an increase in diabetes technology uptake and improved diabetes self-management habits, which are independently associated with improved glycaemic and quality-of-life outcomes [107, 135, 142–144].

Finally, addressing psychosocial factors in low socioeconomic and minority race and ethnic groups who have a disproportionately larger burden of depression, diabetes distress, and other psychosocial concerns may be yet another way to bridge the disparities seen in paediatric type 1 diabetes management and outcomes.

Screening and early treatment of risk factors for complications and associated conditions

Dyslipidaemia

Cardiovascular disease is a leading cause of morbidity and mortality in adults with type 1 diabetes. Pre-clinical atherosclerosis often starts in childhood. While children with type 1 diabetes generally have a favourable lipid profile, this remains a major modifiable cardiovascular risk factor in this population. Screening for dyslipidaemia in children with type 1 diabetes should commence after diagnosis, once normoglycaemia has been established, in those older than 2 years of age [145]. If within the accepted risk level (low-density lipoprotein (LDL) ≤100 mg/dl; 2.6 mmol/l), lipids should be repeated at 9–11 years of age.

Per ISPAD and ADA guidelines [146, 147], children with LDL levels >100 mg/dl (≥2.6 mmol) should optimize glucose management and follow dietary and lifestyle interventions. If LDL is 130 mg/dl (≥3.4 mmol/l) and there is one or more cardiovascular risk factors, then statin therapy is recommended for children >10 years of age. Target LDL level is 100 mg/dl (<2.6 mmol/l). Target high density lipoprotein (HDL) is >35 mg/dl (>1.1 mmol/l) and triglycerides 150 mg/dl (<1.7 mmol/l). Approved therapies for children include bile acid sequestrants and statins [145, 148, 149]. Bile acid sequestrants are not well tolerated and therefore the drugs are frequently not taken. Several short-term trials of statins have confirmed their safety and efficacy in children and adolescents with familial hypercholesterolaemia. If therapy with statins is undertaken, regular monitoring of liver function and screening for symptoms of rhabdomyolysis should occur. Appropriate contraceptive advice should be given to girls receiving statins [149].

Microalbuminuria

Microalbuminuria is the first clinical manifestation of diabetic nephropathy and may be reversible with diligent glycaemic and blood pressure management [150]. Microalbuminuria is defined as any of the following:

- Albumin excretion rate 20–200 µg/min, or 30–300 mg/24 h in 24 h urine collections.
- Albumin concentration 30–300 mg/l (in early-morning urine sample).
- Albumin-to-creatinine ratio 2.5–25 mg/mmol or 30–300 mg/g (spot urine) in males and 3.5–25 mg/mmol in females (because of lower creatinine excretion).

Screening for microalbuminuria with a random spot urine sample should occur annually in children when they begin puberty or are 10 years of age (whichever is earlier) and have had diabetes for more than five years. If values are increasing or borderline, more frequent screening should occur. For abnormal results, testing should be repeated. The diagnosis of microalbuminuria requires documentation of two abnormal samples out of three samples over a period of 3–6 months. Once persistent microalbuminuria is confirmed, non-diabetes-related causes of renal disease should be excluded and treatment started. Persistent microalbuminuria is associated with end-stage renal disease and increased risk of macrovascular disease. Treatment with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) should be started in the setting of persistent microalbuminuria, even if the blood pressure is normal [145]. Females of reproductive age should be counselled on the teratogenic effects of ACE inhibitors and ARBs and offered appropriate contraception as needed [151]. Children and their families should be counselled about the importance of optimal glycaemic management and smoking cessation if applicable. ARB blockers are not approved for use in children, but are occasionally used off-label.

Elevated blood pressure

Hypertension in adults with diabetes is associated with the development of both micro- and macrovascular disease. Treatment of blood pressure is critical in reducing these complications in adults and presumably in children and adolescents as well. Blood pressure should be checked and reviewed at each clinic visit. Hypertension is defined as systolic or diastolic blood pressure (measured on at least three separate days) above the 95th percentile for the child's age, sex, and height and target blood pressure is <90th percentile. Care should be taken to ensure use of an appropriately sized cuff in children to avoid inaccurate readings. If elevated blood pressure is confirmed, non-diabetes causes of hypertension should first be excluded. Treatment includes lifestyle interventions and ACE inhibitors or ARBs if lifestyle fails [151].

Retinopathy

Adolescents have a higher risk of progression to severe non-proliferative or proliferative retinopathy compared to adults with diabetes, although there is a low risk of development <12 years of age [152, 153]. The first dilated ophthalmological examination should be obtained by a healthcare professional trained in diabetes-specific retinal examination once the child is ≥10 years old or at puberty (whichever is earlier) and has had diabetes for

3–5 years [147, 154]. The frequency of subsequent examination is generally every two years, but may be spaced to four years with a favourable individual risk profile and advice of an eyecare provider [151, 155].

Neuropathy

Although peripheral neuropathy is extremely rare in children with 1–2 years of diabetes, the SEARCH for Diabetes in Youth study found a 7% prevalence of peripheral neuropathy in children with type 1 diabetes [156]. Therefore children with diabetes should have an annual foot exam starting at age 10 years or the start of puberty (whichever is earlier) after the child has had diabetes for 5 years, including inspection and determination of monofilament sensation, as well as assessment of presence of neuropathic pain. This can also be an opportunity to begin to educate the young person on proper foot care [157].

Coeliac disease

The prevalence of biopsy-confirmed coeliac disease in children with type 1 diabetes ranges from 1% to 10%, compared to <1% in the general population [154]. Clinical manifestations of coeliac disease can include delayed growth and puberty, decreased bone mineralization, abdominal pain, and abnormal liver function tests, which may overlap with those with persistent hyperglycaemia.

All children should be screened for immunoglobulin(Ig)A transglutaminase autoantibodies at the onset of diabetes and, if negative and asymptomatic, rescreened within two years of diagnosis and again after five years since diagnosis. Children with symptoms or a first-degree relative with coeliac disease may benefit from more frequent screening. If the transglutaminase autoantibodies are negative, but the child has symptoms and/or signs consistent with coeliac disease, other causes (e.g. hyperglycaemia, or intolerance of milk, soy, or salicylates) should be explored. If transglutaminase autoantibodies are strongly and persistently positive (radioimmunoassay index >0.5 or enzyme-linked immunosorbent assay [ELISA] >60), biopsy is recommended even in a completely asymptomatic child. By contrast, children with low to moderately positive transglutaminase autoantibody levels may have a false-negative biopsy and may be falsely reassured that they do not have coeliac disease and forgo further follow-up.

Untreated coeliac disease may pose problems with diabetes management, including inconsistent nutrient absorption, increased risk of hypoglycaemia, and chronic diarrhoea that is difficult to differentiate from that caused by autonomic neuropathy in adults. Gluten-free diets may prevent some of the episodes of hypoglycaemia. The benefit of early detection and treatment remains unproven, but is the subject of ongoing investigation.

Thyroid disease

Hypothyroidism is present in 3–8% of children with type 1 diabetes. Long-term follow-up suggests that as many as 30% of people with type 1 diabetes develop autoimmune thyroiditis. The presence of hypothyroidism has been associated with thyroid autoantibodies, which are observed more frequently with increasing age and diabetes duration and female sex. With follow-up of 20 years, 80% of people with type 1 diabetes and thyroid peroxidase (TPO) autoantibodies develop hypothyroidism. Hyperthyroidism is less common than hypothyroidism in people with type 1 diabetes, but still more common (3–6%) than in the general population.

The presence of autoimmune thyroiditis in the population with type 1 diabetes has the potential to affect growth, weight gain, diabetes management, menstrual regularity, and overall well-being. All children with type 1 diabetes should be screened for elevated levels of the thyroid-stimulating hormone (TSH) after stabilization at onset of diabetes and every 1–2 years thereafter, or sooner if symptoms of hypothyroidism or hyperthyroidism are present. TPO antibodies, anti-thyroglobulin antibodies, and free T4 may also be sent at the time of TSH screening [89]. Those with positive TPO autoantibodies and normal thyroid function should be screened on a more frequent basis (every 6–12 months). Treatment of thyroid disease in children with type 1 diabetes is the same as for the general population.

Addison disease

Addison disease affects approximately 1 in 10 000 of the general population and 1% of people with type 1 diabetes [158]. While there are currently no data to support routine screening for Addison disease, the increased risk of this disease necessitates a heightened degree of suspicion on the part of the clinician should any signs or symptoms of Addison be present, particularly in the setting of frequent, severe, or unexplained hypoglycaemia. Most children who develop disease are mildly symptomatic with decreasing insulin doses and HbA_{1c}. Adrenocorticotropic hormone (ACTH) stimulation testing remains the gold standard for diagnosing adrenal insufficiency, although increased risk can be ascertained by the detection of autoantibodies reacting to 21 hydroxylase (21-OH). The presence of this autoantibody in the general population is very rare, in contrast to 1–2% in people with type 1 diabetes. Of those with positive antibodies, but as yet free of Addison disease, 15% develop Addison disease within a few years.

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70 Adolescence and Emerging Adulthood: Diabetes in Transition

Charlotte W. Chen and Lori M.B. Laffel
Pediatric, Adolescent and Youth Adult Section, Joslin Diabetes Center, and Harvard Medical School, Boston, MA, USA

Key points

- The period of adolescence and emerging adulthood involves significant physical, social, and emotional growth, and presents unique challenges to those with diabetes.
- The intensive treatment required for consistent and effective diabetes care, especially for young people with type 1 diabetes, can be time-consuming and challenging for young adults with diabetes. It can be especially challenging as adolescents move towards adulthood. The degree of independence and responsibility adolescents accept for their diabetes care ideally increases as they enter older adolescence and young adulthood.
- Empowering emerging adults with a sense of self-efficacy with respect to their capacity to care for diabetes effectively is crucial to ensuring success during this transitional phase and in establishing consistent self-care habits for life.
- As the emerging adult is likely to leave the home, the supportive role originally assumed by parents and family members can be taken on by close friends and significant others.
- The process of transition followed by the actual transfer from paediatric diabetes care to an adult practice can be challenging for emerging adults with diabetes. It is imperative that parents and the paediatric diabetes team members provide the necessary training and preparation for self-care to support the transfer to an adult practice. It is recommended that parents continue to support their teenagers' diabetes care during this tumultuous developmental stage.
- Parents of teenagers along with healthcare professionals should monitor and attempt to prevent burnout from diabetes care. Inclusion of diabetes educators and mental health clinicians on the adolescent and emerging young adult's diabetes team can help reduce the likelihood of burnout and help overcome barriers to self-care acquisition.

Although this chapter focuses on the adolescent and young adult with type 1 diabetes, the commonest type of diabetes affecting this age group, many of the issues also apply to young people with type 2 diabetes. Thus, the chapter will describe the process of transition that begins during adolescence and culminates in the transfer from a paediatric care team to an adult diabetes or endocrinology practice for young people with either type 1 diabetes or type 2 diabetes. This period of transition is affected by multiple developmental changes that teenagers undergo between the ages of 13–18 years, with additional developmental issues arising during the stage of emerging adulthood, between the ages of 18–25 and 25–30 years. The chapter will examine the psychosocial and physical changes experienced by adolescents as well as the special challenges teenagers and emerging young adults with diabetes encounter as they transition from adolescence into early adulthood.

The process of transition requires the growing and developing adolescent to take on responsibilities for diabetes self-care, tasks that were previously managed by the parents. This process should be gradual, with sharing of diabetes management between parents and teenagers initially, followed by the ultimate transfer to self-care that should precede the time when the older adolescent or emerging young adult leaves the paediatric diabetes team and receives care from a medical team that specializes in adult diabetology or endocrinology.

There is no exact age at which the young person with diabetes should perform all self-care; rather, this is a process that needs to be individualized, depending on development stage, maturity, family support, family expectation, education from the healthcare team, as well as other factors. Acquisition of self-care can begin for some youngsters in the higher primary grades or during the middle school years, although adults may continue to supervise diabetes management tasks. These may include using a continuous glucose monitoring (CGM) device or checking blood glucose levels, assessing the carbohydrate content of meals or snacks, or reading the values on food packages and participating in calculating insulin doses, or even use of an automated insulin delivery device. Participation in these management tasks is generally encouraged by parents and the paediatric diabetes team, with decreasing supervision by parents and other adults from around the ages of 12 or 13 years [1]. There is an additional need to navigate how older adolescents and young adults maintain or discontinue sharing their diabetes self-care activities with parents, especially, for example, given current opportunities for real-time CGM data sharing [2].

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Direction and support provided by members of the paediatric diabetes team are imperative to promote the gradual transfer of these self-care tasks to the teenager, with the goal of maintaining optimal self-management and maximizing the opportunities for achieving target glycated haemoglobin (HbA_{1c}) values and reducing the likelihood of acute and chronic diabetes-related complications [3]. As adolescents differ in their cognitive capacity to perform diabetes tasks with increasing independence, it is imperative that healthcare professionals, parents, and the young person with diabetes work together to establish realistic goals. Helping the growing and developing teenager to develop a sense of self-efficacy in performing diabetes self-management tasks with increasing independence is critical, certainly prior to the transfer to adult diabetes clinics, where healthcare professionals expect independence in diabetes care. The eventual goal is for the adult with diabetes to have the capacity and to possess the skills to engage in full and effective diabetes self-care, having traversed adolescence without diabetes burnout [4].

Demographic information about diabetes

Currently in the USA, about 210 000 children, adolescents, and young adults (<20 years old) are living with diabetes [5]. There appears to be a significant increase in the occurrence of type 1 diabetes and type 2 diabetes in this age group. According to the SEARCH for Diabetes in Youth study in the USA from 2001 to 2012, the incidence rate of young-onset type 1 diabetes increased by 1.4% annually [6]. For type 2 diabetes, the incidence rate increased by 7.1% annually, with a high relative increase in racial and ethnic groups compared to non-Hispanic white people [6, 7]. An analysis of EURODIAB registry data from over 26 European centres found that the incidence rate of type 1 diabetes increased by 3.4% annually over 1989–2013 [8]. A paper from Lawrence et al. shows that the prevalence of type 1 diabetes and type 2 diabetes was also increasing for 2001–2017. Type 1 diabetes has a relative increase of 45.1% over 16 years, while type 2 diabetes has a relative increase of 95.3% over 16 years, and the most significant increase was noted in non-Hispanic Black and Hispanic young people [9].

Physical changes during adolescence

At the same time that there is an expectation for the teenager to take on increasing responsibility for diabetes self-management, the young teenager is undergoing substantial physical, developmental, behavioural, and emotional changes, many of which substantially affect insulin needs. The major change in diabetes management results from the recognized insulin resistance associated with pubertal growth and development (Chapter 69) [3, 10]. Regardless of the age at diagnosis of diabetes, this period of adolescence requires great vigilance to assess diabetes needs and direct management due to physical and lifestyle changes. This vigilance entails frequent blood glucose monitoring, attention to carbohydrate intake, physical activity that becomes as much therapeutic as recreational in nature, and, of course, careful attention to insulin delivery in terms of both amount and timing. Shortly after diagnosis, people with type 1 diabetes generally experience a time-limited phase known as the *honeymoon* stage, during which the pancreatic β cells continue to produce a small amount of insulin. As time progresses, the pancreas produces less insulin, and those with type 1 diabetes experience increasing needs for exogenous insulin as the honeymoon wanes. This intensification of type 1 diabetes management can be particularly apparent for the growing and developing adolescent, whose insulin needs usually increase rapidly during puberty by up to 50% or even more [3, 10].

To manage insulin effectively for an adolescent, parents and the paediatric diabetes team need to pay close attention to changes related to puberty, weight gain, and linear growth. Insulin doses need to be increased to help ensure that the HbA_{1c} remains within the target range of <7.0% (<53 mmol/mol) set by the International Society for Paediatric and Adolescent Diabetes (ISPAD) and American Diabetes Association (ADA) [11, 12], and for those using CGM, that the glucose time in range is 70–180 mg/dl (3.9–10 mmol/l) and remains >70% without substantial hypoglycaemia [13].

Thus, while teenagers with diabetes experience increasing independence in many aspects of their lives related to school and social life, the period of pubertal growth and development requires ongoing parent involvement in diabetes management to ensure that glycaemic levels do not deteriorate. Indeed, teamwork in diabetes management between parents and teenagers is recommended at this stage. Furthermore, frequent consultation with members of the paediatric diabetes team regarding insulin adjustments, appropriate nutrition, stress management, and exercise also reduces the likelihood of hyperglycaemia, glucose variability, and the development of acute complications [3, 10].

Developmental stages

This section of the chapter will describe the normal developmental stages of adolescence and emerging adulthood, with a focus on various transitions and recommendations for optimal family management of diabetes (Table 70.1). Key developmental changes that may affect the ability of the teenager and young adult with diabetes to engage in self-care tasks independently will be reviewed (Figure 70.1). There will also be a section on empirical evidence for specific intervention and care strategies for adolescents and emerging adults with diabetes. Lastly, novel technology platforms to support optimal diabetes management will be discussed.

Adolescence (age 13–18 years)

Along with rapid physical growth, cognitive development, and pubertal maturation, adolescence is a time of increased attention to body image and sexuality. Teenagers within this age range are also forming their identities, a process that can lead to increases and decreases in taking on and accepting greater responsibility for various school and home-related tasks. Furthermore, relationships with same-age peers have a powerful influence on an adolescent's behaviour [14–16].

A tremendous number of physical, social, and emotional changes occur during the period of adolescent growth and development, often challenging the management of diabetes, their parents, and the healthcare team. The ADA and ISPAD, along with other organizations, recommend an HbA_{1c} goal of <7.0% (<53 mmol/mol) [11, 12]. These societies also recommend more stringent HbA_{1c} goals (such as <6.5%; <48 mmol/mol) for young people with type 1 diabetes and type 2 diabetes who can achieve these targets without significant hypoglycaemia or undue burden of care [12, 17]. The National Institute for Health and Care Excellence (NICE) guidelines include an HbA_{1c} goal of ≤6.5% (48 mmol/mol) [18].

Table 70.1 Developmental stages and major developmental tasks during adolescence and emerging adulthood.

	Typical development	Diabetes-specific development	Psychosocial challenges
Early adolescence (ages 13–15 yr)	Rapid growth Sexual maturation Body image concerns Changing physical activity level Social/friend interactions Interest in technologies Ongoing cognitive development Emerging alcohol and drug experimentation	Frequent alterations in glucose levels Expanding needs for self-care and sharing diabetes responsibilities between teenager and parent Body image concerns related to wearing diabetes devices Concerns regarding peer awareness and comments about diabetes Understanding exercise and diabetes needs	Diabetes-related family conflict Disordered eating Depressive symptomatology Fear of hypoglycaemia or hyperglycaemia School staff knowing what to do in an emergency Family planning
Later adolescence (ages 16–18 yr)	Identity formation Sexual activity Body image concerns Changing physical activity level Social/friend interactions Interest in technologies Ongoing cognitive development Emerging alcohol and drug experimentation	Balancing type 1 diabetes care with schoolwork and social interests Greater independence and need for adult support related to diabetes care Body image concerns related to wearing diabetes devices Concerns regarding peer awareness and comments about diabetes Understanding exercise and diabetes needs	Diabetes-related family conflict Disordered eating Depressive symptomatology Fear of hypoglycaemia or hyperglycaemia School staff knowing what to do in an emergency Family planning Driving a motor vehicle
Early phase emerging adulthood (ages 19–24 yr)	Education and career training Moving away from the family home Dormitory/apartment roommates Changes in emotional and financial ties with parents Wider friendship group	Possible gaps in medical insurance Making time for type 1 diabetes when with friends Negotiating performing diabetes tasks at first job or while at college Remembering to refill/reorder prescriptions Recreational substance use Negotiating self-advocacy	Diabetes-related family conflict Disordered eating Depressive symptomatology Fear of hypoglycaemia or hyperglycaemia Teachers or co-workers knowing what to do in an emergency Family planning
Later phase emerging adulthood (ages 25–30 yr)	Interest in marriage, starting a family Further career advancement Expanding social, emotional, and financial independence	Increasing awareness of the impact of diabetes care on significant others, family planning, and career development Recreational substance use Negotiating self-advocacy Remembering to refill/reorder prescriptions	Diabetes-related family conflict Health roles of close friends or significant others Lecturers and co-workers knowing what to do in an emergency Family planning

However, of all age groups, adolescents are farthest away from this target HbA_{1c} goal [19]. Along with the impact of pubertal development, physical growth, and emotional stress that most adolescents experience, diabetes, and especially type 1 diabetes, when compared to other chronic illnesses of childhood, requires the teenager to perform management tasks multiple times each day, day in and day out without any break. In addition to checking blood glucose levels, attending to food intake, administering insulin, understanding the impact of exercise on glucose levels, adolescents with diabetes and their families also must navigate the impact of acute illness on their diabetes management needs [1]. Teenagers develop emotional maturity and the ability to take on diabetes responsibilities with independence at varying rates and at various ages. However, some teenagers do not possess the emotional maturity to sustain tasks of daily self-care, and some may experience gaps in medical care, which can lead to adverse health outcomes [20].

Family support, family involvement in diabetes management, and low levels of diabetes-specific family conflict are associated with smoother transitions for adolescents as they acquire and accept more responsibilities of type 1 diabetes self-care [21–24]. While adolescents with diabetes learn to adapt to fewer adult prompts to engage in and perform self-care tasks accurately and consistently, parents are encouraged to remain involved in sharing management responsibilities. The roles and responsibilities that parents keep versus those that they pass on to the adolescent will differ depending on the adolescent's cognitive capacity and willingness to engage in care activities. As these factors are rarely static due to ongoing maturation and situational stressors experienced by the adolescent and/or family, the roles parents and teenagers fill during this transition will frequently need to be renegotiated. Members of the adolescent's diabetes team can serve as an excellent resource in problem solving the division of responsibilities and ensuring that teenagers with diabetes are provided with a realistic number of self-care tasks. The ultimate goal is for the adolescent to possess a sense of self-efficacy and the capacity to accept and treat diabetes optimally [1].

Additional important factors for an optimal transition of diabetes management from parents to the adolescent include the establishment of self-efficacy and self-advocacy for the teenager, especially in the context of developmental and social needs. Teenagers with a strong belief and confidence that they can perform self-care and advocate for themselves in particular situations are more likely to overcome barriers to diabetes self-care. Teenagers should be empowered to speak up for their diabetes self-management needs in public settings, such as school or sports clubs, and have confidence in doing so. There are improved outcomes when there is acceptance of self-care leading to improved glycaemia [25–27]. In a 2014 study, Wiebe et al. found that adolescents who reported a decrease in

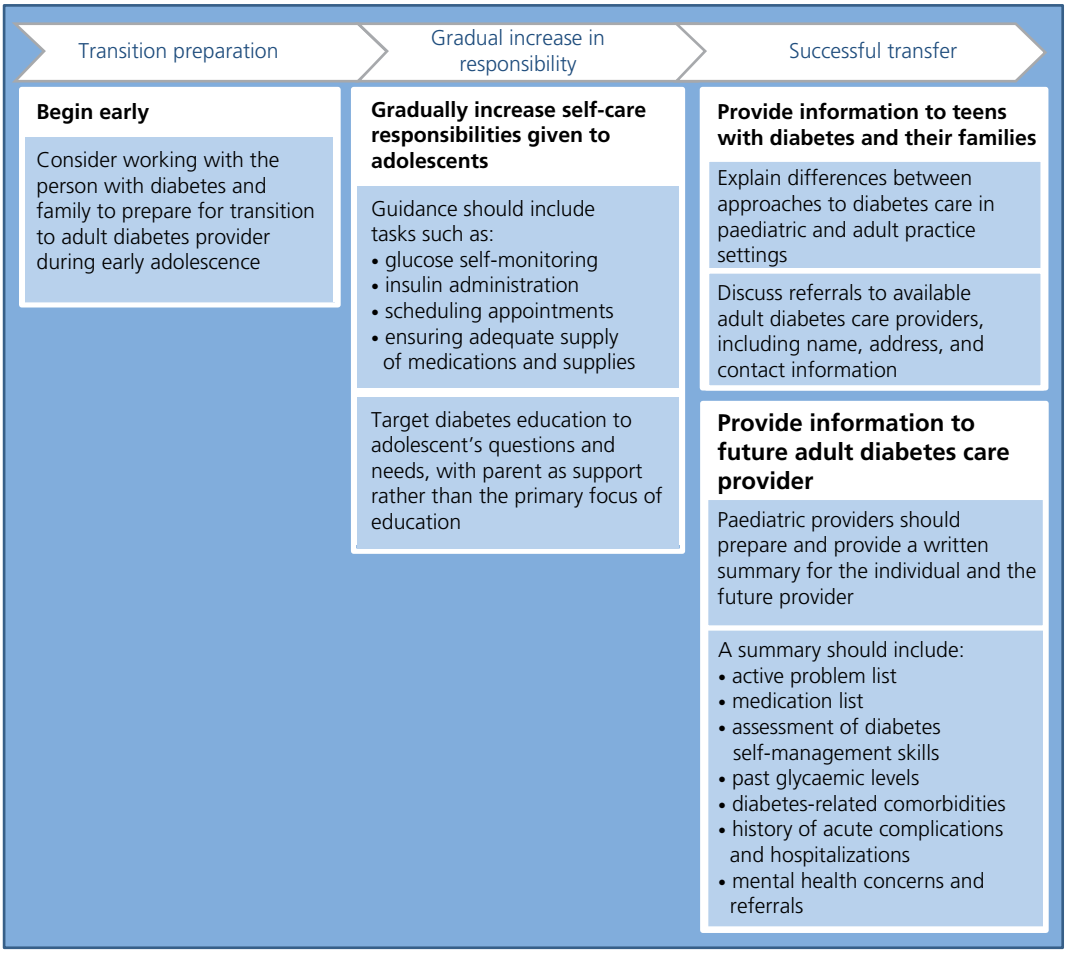

Figure 70.1 Trajectory of transition preparation, self-care acquisition, and transfer to adult care.

parental involvement for type 1 diabetes care and a high sense of self-efficacy were better able to maintain diabetes self-care than those with a lower sense of self-efficacy [28]. Those who possessed a lower sense of self-efficacy had better glycaemic levels only when a parent played a greater role in establishing self-care skills [29]. These findings support the need for the adolescent's diabetes team to consider the level of self-efficacy an adolescent possesses when increasing their self-care independence.

In addition to the impact of pubertal insulin resistance, other factors can lead to deterioration in glycaemic levels. Glycaemic targets can be challenging when teenagers have competing preoccupations, for example with athletics, academic studies, and social distractions, which can detract from self-management, leading to lower self-care and more inadequate glycaemic levels [10, 23, 30, 31].

Based on a T1D Exchange study in 2019, adolescents from 13 to 17 years old had a mean HbA_{1c} of 9.2% (77 mmol/mol), with only 17% achieving HbA_{1c} levels <7.5% (<58 mmol/mol) [19]. In the same report, a majority of the adolescents 13–17 years old (79%) disclosed missing insulin bolus doses. Furthermore, 40% of the adolescents receiving injection-based therapy reported missing basal insulin at times [19]. In 2013, Hilliard et al. analysed predictors of glycaemic deterioration in 150 adolescents with type 1 diabetes over a period of 18–24 months [32]. Approximately two-thirds of participants did not meet the requirement to check blood glucose values more than four times daily and did not achieve the target HbA_{1c} of <7.5% (58 mmol/mol). There were both modifiable and non-modifiable factors related to the suboptimal management and glycaemic outcomes. Non-modifiable factors included ethnic minority status and unmarried caregiver status. The authors highlighted that diabetes healthcare professionals should identify these non-modifiable factors to assess a person's risk and provide timely support. The modifiable factors associated with deteriorating type 1 diabetes care and glycaemic levels included injection-based insulin regimens as well as diabetes-specific family conflict [32]. Similarly, there are factors associated with diabetes device use in adolescents with type 1 diabetes. Chen et al. found that pump and CGM users were more likely to have more favourable psychosocial, sociodemographic, and diabetes self-care characteristics compared with non-device users [33].

These observations emphasize the importance of including behavioural and mental health assessments as part of adolescent diabetes care visits to assess for and intervene in stressful parent–teen interactions and modifiable barriers related to diabetes management, while providing additional support to those with non-modifiable barriers to benefit the transition to self-care for teenagers with type 1 diabetes.

Social context can have an important impact on an adolescent's diabetes self-management. Those who are extremely peer oriented may perceive diabetes as a barrier that prevents them from engaging in peer activities [34]. Borus et al. conducted a study where,

over a 14-day period, adolescents with type 1 diabetes, aged 14–18 years, carried handheld devices that prompted them to report social context variables related to self-monitoring of blood glucose. Despite concern that many adolescents with type 1 diabetes do not check their blood glucose as often as recommended, the study demonstrated an increased likelihood of participants checking blood glucose levels when the teenagers expressed a strong desire to blend in with peers and a lower likelihood of checking blood glucose levels when the teenagers wanted to impress others. The authors suggested that these findings could help diabetes teams to encourage teenagers to check their glucose levels more frequently, as monitoring allows them to identify out-of-range glucose values promptly, thereby allowing them to avoid possible embarrassment as a result of sudden unexpected hypoglycaemia or symptomatic hyperglycaemia [35].

Adolescence is a time for experimentation and engaging in risky behaviours such as alcohol, tobacco, and substance abuse [36]. Potter et al. examined the prevalence of alcohol, tobacco, and other illicit substance use in Canadian adolescents with type 1 diabetes compared with a general adolescent population and found that the engagement of teenagers with type 1 diabetes with alcohol, tobacco, and cannabis use was similar to the control group [37]. Another published study from the T1D Exchange reported that the mean age for the first use of an illicit substance was 18 ± 5 years, 17 ± 3 years for first alcohol consumption, and 17 ± 3 years for first tobacco use [38]. Therefore, it is essential to routinely discuss and educate adolescents on the effects of alcohol, tobacco, and illicit drug use in type 1 diabetes.

There have been several family-based behavioural interventions aimed at optimizing glycaemic levels during adolescence. Two behavioural family interventions, family teamwork and behavioural family systems therapy, have reported the most consistent, lasting impact on diabetes outcome [39]. Laffel et al. performed a randomized prospective study examining the impact of a family-focus teamwork intervention on glycaemia and compared it with standard multidisciplinary diabetes care. A year later, they found that those who received the teamwork intervention were less likely to have any deterioration in glycaemic levels and more likely to maintain or increase family involvement without any negative impact on quality of life [40]. Wysocki et al. conducted a six-month behaviour intervention using Behavioural Family Systems Therapy for Diabetes (BFST-D). Participants exposed to this intervention were compared with two comparison groups (educational support and standard care); teenagers in the BFST-D group demonstrated better diabetes self-management at follow-up compared with the comparison groups [41].

Multisystemic therapy targets barriers on multiple levels, such as individual, family, and community, can also be used for adolescents with diabetes with elevated HbA_{1c}. Ellis et al. performed a randomized controlled trial (RCT) evaluating the effect of multisystemic therapy compared with weekly telephone support on glycaemic levels and insulin administration in teenagers with type 1 diabetes and type 2 diabetes. Participants in the multisystemic therapy group experienced a significant reduction in HbA_{1c} at the end of the study and 12 months after the intervention [42].

Another series of studies has focused on cost-effective, clinic-based interventions utilizing *care ambassadors* [43–45]. These care ambassadors do not possess medical training, but they provide support to individuals and families between medical visits, ensuring timely follow-up, which is particularly important when the competing needs of adolescence may impede routine diabetes visits. Those individuals with type 1 diabetes receiving care ambassador support compared with standard care demonstrated increased ambulatory visits, reduced hospitalizations and emergency room visits, and reduced occurrence of severe hypoglycaemia. Furthermore, those with type 1 diabetes and elevated HbA_{1c} at study entry who were assigned to receive care ambassador support compared with standard care demonstrated a decrease in HbA_{1c} [43–45].

Motivational interviewing can be used to bolster an adolescent's willingness to increase self-management. Motivation interviewing involves collaborative communication between a member of the paediatric diabetes team and the adolescent in an effort to strengthen the teenager's personal motivation for change and commitment towards achieving a specific goal [46]. Channon et al. designed and implemented an RCT that studied the impact of motivational interviewing during clinic visits in 66 teenagers with type 1 diabetes, aged 14 and 17 years [47]. Findings of the 12-month study showed that, compared with control participants, those who received the motivational interviewing intervention had lower mean HbA_{1c}. Furthermore, this improvement was maintained a year after the intervention ended. Motivational interviewing may serve a role during transition as a means to motivate support for the acquisition of self-care tasks among teenagers with diabetes.

Several studies have examined the use of mobile technologies to assist adolescents in their transition to diabetes self-care. Text messaging has been studied as means of offering reminders to adolescents for self-care when they are away from their parents and other adult care providers. Markowitz et al. conducted a study where adolescents and young adults with diabetes received text messages that promoted a general healthy lifestyle and diabetes self-care [48]. Messages were tailored to assisting study participants attain personal goals regarding diabetes self-care. While self-efficacy and glycaemic levels did not change during the three-month pilot study, results indicated that text messaging was highly acceptable to participants and could be expanded in future studies [48]. A Scottish study entitled Sweet Talk sent daily automated text messages that reinforced goals that adolescent study participants had set during their diabetes clinic visit [49]. The intervention did not demonstrate consistent improvement in participants' HbA_{1c}, but results suggested that the adolescent participants developed a stronger sense of self-efficacy related to their ability to care for type 1 diabetes.

Given the general increased use of smartphones, studies have also looked at mobile applications to support adolescents' self-management skills and improve glycaemic outcomes. In 2019, Pramanik et al. created a mobile application that reminded adolescents with suboptimally managed type 1 diabetes about insulin, meals, and physical exercise. They found a reduction in HbA_{1c} in the participants who used the mobile application [50]. A similar study, undertaken in 2017 by Goyal et al., also found an increase in daily self-monitoring of blood glucose and improvement in glycaemic levels in adolescents who used *bant* (a diabetes self-management app) compared with the control group [51]. However, these studies lasted 12 months, and it is uncertain if there will be any glycaemic benefits with continued usage. It is important to note that mobile applications need to be engaging and updated to ensure durable and persistent usage by adolescents.

There is also an uptake in social media usage and many adolescents engage in these activities. A qualitative study by Malik et al. found that teenagers appeared to be interested in using social media to increase engagement with their diabetes care team and to support their self-care [52].

Table 70.2 gives details of other clinical interventions that are being tested to improve glycaemia in adolescents with diabetes.

Emerging adulthood

To add to the challenges of transition to self-care during adolescence, another developmental stage, termed *emerging adulthood*, demands the attention of both paediatric and adult diabetes teams. This developmental stage of young adulthood has been popularized over the past 20 years in the USA and other high-income countries [56]. The concept of emerging adulthood developed from observations that many individuals in their late teens and early 20s are delaying tasks that had been traditionally associated with this age, such as marriage, parenthood, and work. These life events now occur for many in their late 20s and early 30s. Emerging adulthood can be separated into an early phase and a later phase. Notably, health insurance coverage for young adults with diabetes has generally not been a problem in countries with universal coverage, but young adults in the USA had been at risk for gaps in health insurance coverage until reforms such as the Patient Protection and Accountable Care Act mandated coverage under parents' policies until the age of 26 years [57].

The early phase of emerging adulthood corresponds to the years immediately after secondary education or high school, between the ages of 18 and 24 years. During this phase, the emerging adult

Table 70.2 Examples of interventions under study worldwide.

Interventions	Trial	Prominent findings/ongoing trial	Country
Art	An open-label 12-wk trial of group art therapy in young adults with type 1 diabetes and type 2 diabetes (NCT02790892) Outcomes: changes in social support and diabetes distress scores	The study had poor attendance Participants who participated in group art therapy had a higher score in social support and lower in diabetes distress [53]	Canada
Behavioural	A randomized controlled trial that tests the efficacy of an emotional abilities training programme (NCT03734367) Outcomes: change of emotional skills of young people with type 1 diabetes	Ongoing	Spain
Group education	A randomized open-label trial that evaluated the impact of group diabetes education in teenagers with type 1 diabetes (NCT03147274) Outcomes: frequency of blood glucose monitoring	The intervention group demonstrated significantly improved diabetes self-delicacy and transition readiness [54].	USA
Mobile	A randomized open-label trial that tests the efficacy of my MyT1DHero mobile application (NCT03521362) Outcomes: change in glycaemic levels, diabetes knowledge, and family communication	Ongoing	USA
Mobile	A randomized open-label trial that evaluated a smartphone application that can determine carbohydrate content using pictures/speech (NCT04354142) Outcomes: assessing carbohydrate counting accuracy and efficiency	Participants using iSpy demonstrated improved carbohydrate counting accuracy and positive acceptability [55]	Canada
Peer mentorship	A randomized trial to test the efficacy of peer mentorship during the transition period (NCT04247620) Outcomes: change in glycaemic levels and time to first adult visit	Ongoing	USA
Peer mentorship	A randomized open-label trial that evaluated the benefits of peer mentorship for parents with youth with type 1 diabetes (NCT03199716) Outcomes: frequency of blood glucose monitoring	Results pending	USA
Pet ownership	A randomized open-label trial that evaluated the impact of pet ownership on glycaemic control for youth with type 1 diabetes (NCT01733524) Outcomes: change in glycaemic levels and healthcare burden	Results pending	USA
Video game	An open-label trial to evaluate the contribution of a computer game (DIVE) in diabetes education (NCT03520855) Outcomes: change in glycaemic levels and self-care skills	Ongoing	France

Source: Information from https://clinicaltrials.gov.

may be physically moving away from home and beginning to change the degree and nature of emotional and financial ties with parents, although the emerging adult is not yet fully independent. During this phase, the young adult experiences tremendous pressures related to academic studies, occupational choices, and social commitments, while separating from the family [57]. Thus, it is not surprising that these competing needs for time, energy, and effort often detract from diabetes self-care, leading to further deterioration in insulin administration and glycaemic levels. Indeed, data from the T1D Exchange Clinic Registry in the USA indicate that HbA_{1c} reaches its peak of 9.3% (78 mmol/mol) during this phase of development [19]. Thus, paediatric and adult healthcare professionals working with emerging young adults must be aware of these competing demands and help to ensure that young adults with diabetes receive reinforcement for self-care behaviours, along with ongoing education and training in self-management, including how to fill prescriptions and make diabetes follow-up appointments [58].

During the later phase of emerging adulthood, usually occurring between the ages of 25 to 30 years, the young adult starts to assume more traditional adult roles [56]. An increasing sense of maturity leads many emerging young adults in the second phase to realize the importance of monitoring their health. Interest in getting married, raising children, and establishing a career leads many individuals to invest more effort in improving self-care and achieving better glycaemic levels [57]. It is no surprise that there is a steady decrease in HbA_{1c} to 8.0% (64 mmol/mol) by the age of 28 years [19]. Considering the young person's increased awareness of self-care needs and health outcomes, this period is ideal for the diabetes team to bolster diabetes management habits. As transfer from paediatric to adult providers likely occurs during this developmental stage, both paediatric and adult healthcare professionals should be well versed in the relevant issues [57].

Changes in family involvement

Family involvement is a critical component of diabetes management during childhood and adolescence. Additionally, parents and family members, as well as members of the paediatric diabetes team, play significant roles in helping adolescents and young adults transition to take on the primary role of managing their diabetes. Interestingly, the perceptions of parents may contrast at times with those of the paediatric diabetes team with respect to a young person's capacity to engage independently and effectively in self-care. Wysocki et al. had parents and members of paediatric medical diabetes teams complete surveys that measured their estimates of the self-care independence of young people with type 1 diabetes [59]. This study, which was conducted across multiple type 1 diabetes centres, found that compared with parents, healthcare professionals characterized young children and those in elementary school as less capable of independently monitoring and treating type 1 diabetes without the supervision of an adult caretaker. Parents of these children reported earlier mastery of skills by their children related to motor activities (e.g. blood glucose self-monitoring) and the capacity to take care of type 1 diabetes events with immediate consequences (e.g. preventing or treating hypoglycaemia). Additional results indicated that many parents of adolescents, however, reported lower levels of self-care and competence for critical skills involving executive functions. These self-care activities included planning, anticipation, and self-regulation (e.g. preventing hyperglycaemia or adjusting insulin doses) [59].

Before 1986, no guidelines existed for the family sharing of type 1 diabetes management activities or what tasks were appropriate at different ages and stages of development. Ingersoll et al. found that as children grew older, responsibility for type 1 diabetes tasks shifted from the parent to the growing teenager [60]. This finding matches the general developmental expectation that adolescents will require less guidance in general from teachers, for example, to write down homework assignments and fewer prompts from parents to complete homework. However, when parental involvement in diabetes management tasks decreased, specifically regarding adjusting insulin, Ingersol et al. reported that adolescents did not increase their independence and effectiveness in the self-care management of type 1 diabetes. Nevertheless, those who took over more responsibility for insulin adjustments were at 'advanced levels of cognitive maturity and had a stronger personal sense of control over diabetes' [60]. These findings launched a critical body of research related to family teamwork during adolescence, which has changed the paradigm of care during this stage of development and highlights the need to individualize approaches based on the individual's cognitive, emotional, and social development.

As parental involvement in type 1 diabetes care declines over time, the roles of the child or teenager and family in diabetes management rarely remain static; the growing and developing child goes from a stage of dependence on parents or other adults, to sharing tasks or a state of interdependence, prior to emerging with complete independence in self-care during later adolescence and young adulthood. To provide optimal care, paediatric diabetes providers are encouraged to be well versed in the ebb and flow of the roles of the adolescent and family members during the course of development. Normal developmental tasks of childhood and adolescence call for slowly increasing the young person's acquisition of responsibilities, personal decision making, and self-care (Figure 70.1) [61]. Division of type 1 diabetes management roles within the family is often directed by the multidisciplinary diabetes care team, which ideally provides ongoing education and psychological support for teenagers with type 1 diabetes and their families, with a need to direct diabetes education and support to both the teenager and the parent. Healthcare team members can provide anticipatory guidance and realistic expectations related to the roles of the young person and family members [3].

It is important to recognize that adolescents and emerging adults will likely differ in their capacity to perform diabetes self-management independently. The ability to manage diabetes responsibilities can be affected by executive functioning challenges, such as attention-deficit/hyperactivity disorder (ADHD), as well as short-term and working memory difficulties [62]. Several recent studies have focused on the impact that hypoglycaemia and hyperglycaemia may have on cognitive ability and executive functioning skills [63, 64]. The findings have been mixed, and deeper examination of these studies is beyond the scope of this chapter. Nonetheless, it is important to consider the impact of ADHD, short-term/working memory, executive functioning, and organizational skills on an adolescent's or emerging adult's capacity to perform diabetes self-care independently, consistently, and effectively. Dysfunction in executive functioning in young people with type 1 diabetes not only affects diabetes self-care and glycaemic levels, but also has impacts

on the health-related quality of life, especially in females [65]. The individual may benefit from carrying a discrete, step-by-step checklist or from utilizing mobile alarms as reminders or aids to perform diabetes tasks as the young person acquires increasing independence in self-care. Depending on the skill level of the teenager or young adult, the checklist or reminder can include instructions for what to do when blood glucose levels are out of range, either low or high.

To increase the likelihood that adolescents and young adults with diabetes will experience success in self-care, it is imperative that parents and members of the paediatric diabetes team monitor and take action to prevent or intervene for diabetes burnout. Research has suggested that several factors, including low self-efficacy, low self-esteem, complex treatment regimens, and longer duration of disease, contribute to burnout [66, 67]. Burnout in adolescents becomes evident when teenagers reduce their frequency of blood glucose monitoring and glycaemia subsequently deteriorates [68]. Members of the adolescent's diabetes team, specifically diabetes educators and mental health counsellors, can help parents and teenagers identify and manage diabetes burnout and ensure parents remain in supportive roles when the adolescent experiences this challenge during transition to greater self-care.

Diabetes technologies

Despite the burgeoning of new technologies to assist in managing diabetes, especially type 1 diabetes, over the past 20+ years, consistent and effective use of devices, such as insulin pumps and CGM, can be challenging for people with diabetes across the age range. Insulin pumps can offer ease of insulin delivery throughout the day and night. Several closed-loop or hybrid closed-loop systems on the market can adjust specific aspects of insulin delivery to help the user achieve glycaemic target levels, such as Control IQ (Tandem Diabetes Care, San Diego, CA, USA) and MiniMed™ 770G (Medtronic, Northridge, CA, USA). A large multicentre RCT in 2019 showed that using a closed-loop system was associated with a greater percentage of time spent in range and reduced hypoglycaemia in adolescents and young adults compared with a sensor-augmented insulin pump [69, 70].

CGM devices can enable people with diabetes to monitor trends in glucose levels and to receive alerts and alarms when glucose values fall out of range [71, 72]. In the USA, Dexcom CGM version G5 and higher (Dexcom, Hudson, OH, USA) is approved for non-adjunctive use [73]. In addition, there is even an implantable CGM system called Eversense® (Senseonics, Germantown, MD, USA) that can last up to 90 days [74].

However, such devices all require input and vigilance to ensure proper functioning. Thus, the additional effort needed to use these advanced diabetes technologies may impede uptake or lead teens and emerging adults to discontinue them. Published data have identified characteristics related to the underuse of these advanced technologies, such as lower socioeconomic status and adolescence [75]. Adolescents and young adults have the highest rate of insulin pump discontinuation compared with other age groups in the T1D Exchange Clinic Registry [76]. The commonest reasons for discontinuation included problems with wearability and disliking the pump [76]. The healthcare team can help by providing families, adolescents, and emerging adults with realistic expectations and ongoing education and support regarding using these technologies to maximize their update and durability of use. This support should include discussions regarding the optimal timing of initiation of these devices. Similar approaches will likely be needed for soon to be available automated insulin delivery in an artificial pancreas, as human input will remain critical for proper functioning and surveillance of such systems.

Type 2 diabetes in adolescence and transition

Unlike type 1 diabetes, where pancreatic β cells cease to produce insulin, individuals with type 2 diabetes have a combination of reduced insulin sensitivity and defective insulin secretion [77]. Although type 2 diabetes was generally considered a disorder associated with middle or older age, the increased occurrence of childhood obesity over the past few decades has led to a substantial increase in the number of young people diagnosed with type 2 diabetes [78]. Published data show that developed countries such as China and the USA have the highest prevalence of young-onset type 2 diabetes, with 520 cases per 100 000 people and 212 cases per 100 000 people, respectively [78]. Studies from the USA and UK found an increased incidence of young-onset type 2 diabetes among certain race and ethnic groups, including Black, Hispanic, Asian/Pacific Islander, and Native American people [7, 79]. It is particularly concerning that young people diagnosed with type 2 diabetes are at increased risk for more severe diabetes complications (diabetic kidney disease, retinopathy, and peripheral neuropathy) compared with those with type 1 diabetes [80]. In addition, young people with type 2 diabetes have a more accelerated decline of β-cell function at ~20–35% annually compared with older individuals with type 2 diabetes [81, 82].

Treatment for young-onset type 2 diabetes should encompass lifestyle modifications, pharmacological treatment, and diabetes self-management education. Even though lifestyle modification is essential, it is often inadequate in achieving and maintaining glycaemic targets [77]. Therefore, it is important to add pharmacological intervention early on. The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study is the largest clinical trial examining the management of young people with type 2 diabetes [81]. This study enrolled 699 participants, aged 10–17 years old, with recent-onset type 2 diabetes. After a run-in period during which metformin was used to attain an HbA_{1c} <8% (64 mmol/mol), participants were randomized to treatment with metformin alone, metformin with a lifestyle intervention, or metformin with rosiglitazone. About half of the participants experienced the primary outcome of loss of glycaemic control (defined as $HbA_{1c} \geq 8\%$ [64 mmol/mol] for six months or metabolic decompensation requiring treatment with insulin), over an average follow-up of about four years. Loss of glycaemic control occurred at approximately equivalent rates in the metformin alone and metformin plus lifestyle groups, while the group receiving rosiglitazone in addition to metformin had superior outcomes, with a ~25% reduction in the proportion of participants randomized to that group reaching the primary outcome. This was a significant finding, which highlighted the need for treatment of young people with type 2 diabetes with more than one anti-diabetes agent; however, rosiglitazone and other thiazolidinedione drugs are not approved by the US Food and Drug Administration (FDA) for use in children.

Recently, a study by Tamborlane et al. found that liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, with metformin

is efficacious at improving glycaemic levels in children with type 2 diabetes aged 10–16 years old [83]. As a result, it has been FDA approved for use in children with type 2 diabetes aged 10 years or older. Currently, ongoing clinical trials are evaluating the safety and efficacy of adult-approved therapies, such as sodium–glucose cotransporter 2 (SGLT-2) inhibitors and dipeptidyl peptidase 4 (DPP-4) inhibitor for children with type 2 diabetes [84].

Studies of type 2 diabetes medical care have focused on including a short-term diabetes educational component. The TODAY study provided standardized diabetes education during which teenagers with type 2 diabetes received education not only about pathophysiology, how medications work, and lifestyle guidelines, but also about how to improve their diabetes self-care with focused goal setting. Participants were closely monitored with regard to dosages of injected medication and/or oral medication(s) for diabetes. As this chapter is about ensuring the transition from paediatric diabetes care to adult care and increasing the likelihood that adolescents and emerging adults will establish consistent self-care practices, it is important to acknowledge that all participants in the TODAY study had to complete a 2–6-month run-in period successfully prior to randomization. During this period, which could include a minimum of 6 to a maximum of 12 clinic visits, participants were required to demonstrate ≥80% medication taking for at least six weeks, miss no more than two run-in visits, and maintain an HbA_{1c} of <8% (64 mmol/mol) for at least two months [85]. In order to fulfil these requirements, participants were provided with a significant amount of support, including appointment reminders and follow-up phone calls or text messages from study staff. Despite this support, 24% of the young adults who were screened for the study did not fulfil the requirements of the run-in period and thus were excluded from randomization into the main trial.

It is also important to consider the inclusion of family-based behavioural lifestyle intervention focusing on weight loss or prevention of continued weight gain during the transition process. Several international guidelines recommend a multidisciplinary approach to treating young-onset type 2 diabetes [11, 86]. Hannon and Arslanian reviewed the importance of a multidisciplinary team that could include the individual with diabetes, family, physician, nurse educator, dietician, behavioural specialist, and personnel from the adolescent's school [87]. Although the authors did not go into detail regarding the emerging adults' transition from paediatric to adult diabetes care, they emphasized that the focus should be geared towards individualized therapy, family-based interventions, and pharmacotherapy with the objective of weight loss or prevention of continued weight gain, while optimizing diabetes management and glycaemic levels [87, 88]. The importance of family support was illustrated further in a study looking at barriers to oral diabetes medication for young people with type 2 diabetes. The most commonly cited barrier was forgetting with no reason named (39.3%), and interestingly, the most commonly cited strategy to improve medication taking was family support [89].

The transfer of older teenagers and emerging adults to adult diabetes care may offer a unique opportunity to overcome clinical inertia and revisit a young adult's diabetes treatment regimen by adding another medication to the care plan. This transition period can also be a time full of multiple changes in the young adult's life. The SEARCH for Diabetes in Youth study found that while a majority (57%) of young adults with type 2 diabetes transferred from paediatric to adult care after 18 years old, a substantial portion of them (15%) reported no medical care. Those who reported no medical care were more likely to be uninsured [90]. Similarly, a study looking at healthcare visits pre- and post-transition from paediatric to adult care in young adults with type 2 diabetes versus type 1 diabetes in Manitoba, Canada, found that only 76% of those with type 2 diabetes attended any diabetes-related medical visit in the two years post-transition. Pundyk et al. also saw that diabetes visits attended during the pretransition period predicted the number of visits post-transition in those with type 2 diabetes. In addition, only 45% of those with type 2 diabetes met the criteria for successful transition compared with 70% of young adults with type 1 diabetes [91]. This highlights the need to develop a specific transition plan for young adults with type 2 diabetes focusing on the unique characteristics of young-onset type 2 diabetes and their specific needs.

Family planning and the possibility of pregnancy are of major importance in women with diabetes. As part of the TODAY study, all female participants received counselling on birth control, and were required to use some form of contraception (including abstinence) to participate in the study. Despite that, 10% of female participants became pregnant during the study. Of the pregnancies that were not electively terminated, 26.4% ended in miscarriage, stillbirth, or intrauterine demise, and 21.5% of the live-born infants had major congenital anomalies [92]. Another Canadian study found that girls with type 2 diabetes were more likely to become pregnant during the transition period compared with girls with type 1 diabetes [91]. The transition period and transfer to adult care present a unique opportunity for more exploration and counselling on this topic in order to decrease the frequency of poor maternal and fetal outcomes.

Acute and chronic complications in young adults diagnosed with diabetes in childhood

The commonest acute complications for adolescents and young adults with type 1 diabetes are hypoglycaemia and diabetic ketoacidosis (DKA). Severe hypoglycaemia is associated with cognitive dysfunction and abnormalities in young children with type 1 diabetes [93, 94]. In addition, recurrent hypoglycaemia may lead to hypoglycaemia unawareness (Chapter 40). Diabetes devices may help address this issue, as demonstrated in a study by Ly et al. in which the epinephrine response to hypoglycaemia in adolescents with type 1 diabetes was greater after the use of CGM with hypoglycaemia alarms [95].

Gaffney et al. studied the incidence of DKA during 'emerging adulthood' between 1998 and 2014 and found that the DKA rate increased during emerging adulthood in both the USA and Manitoba, Canada [96]. DKA rates were higher among those of a lower socioeconomic status and adolescent girls [96].

The ADA recommends assessment of the history of acute complications, along with continued education on the prevention of recurrence of acute complications [11]. Adolescents and young adults with type 1 diabetes are at risk for various psychiatric disorders, including depression and eating disorders, and diabetes teams should attend to identifying and intervening for such problems to avoid worsening, particularly at the sensitive time of transition. In addition, the problematic usage of alcohol, tobacco, and illicit drugs at this age can increase the risk of diabetes complications such as DKA [97]. Finally, chronic vascular complications, such as retinopathy, nephropathy, neuropathy, and cardiovascular disease, can begin in childhood and continue or worsen in young adulthood. There is a greater vascular complication risk in those developing diabetes before or during puberty compared with after

puberty [98]. Many organizations regularly publish guidelines regarding screening for such complications [11, 99].

Young people with type 2 diabetes are also at risk of acute complications such as DKA and hyperosmolar hyperglycaemia [100]. In addition, there is an increased risk of a variety of chronic complications and comorbidities, including hypertension, dyslipidaemia, nephropathy, retinopathy, non-alcoholic fatty liver disease (NAFLD), polycystic ovary syndrome (PCOS), depression, and binge eating [100]. The TODAY study found that hypertension, dyslipidaemia, and microalbuminuria were present at baseline and increased by the end of the study [101]. This study group recently published a 10-year follow-up study examining the occurrence of diabetes-related complications in participants in the main trial. More than half of the cohort of young adults (mean age 26.4 ± 2.8 years) had developed at least one complication. The risk factors for developing complications included minority race or ethnic group, hyperglycaemia, hypertension, and dyslipidaemia [102]. This study shows the importance of early aggressive management of hyperglycaemia for young people with type 2 diabetes to preserve health and prevent complications [102]. Young adults with type 2 diabetes may also be at risk for mental health problems, such as depression, decreased quality of life due to early complications, and disordered eating behaviour [77, 103, 104].

What is transition?

Transition is the reorientation that people experience in response to a change. While change is situational, such as moving to a new town or changing jobs, transition is the way in which people respond to the changes they encounter in their lives [105]. Transition is the movement people make through such a disruptive life event in order to continue to live with a coherent, albeit evolving, sense of themselves [106]. Transfer refers to the physical change in the ministration of responsibilities from one individual to another; in this case, the paediatric endocrinologists or diabetologists end their relationships with the person with diabetes, who begins meeting with an adult physician. Transition is a process in which the adolescent or young adult with diabetes prepares for self-care and the future change in diabetes team, while transfer is the actual transfer event. If these activities are managed poorly, failure to engage with adult services decreases the likelihood of regular attendance at diabetes medical centres and increases the likelihood of emergency department use and hospitalizations [107, 108].

Within paediatric healthcare, transition has often been defined as the time when an adolescent or young adult makes a purposeful, planned movement from paediatric to adult care services. It is a multiyear process that should begin in early adolescence. The goal is to optimize health and well-being. To accomplish this, several factors need to be present, including:

- Transition preparation.
- Engagement in chronic disease self-management.
- Actual transfer of healthcare from paediatric to adult systems [4].

The moment of transfer requires a hand-off approach between providers. Successful transition from paediatric to adult services involves the family, and is affected by demographic characteristics, diabetes history, glycaemic levels, self-management, and a sense of self-efficacy and transition preparation [109]. Transition is considered successful when an emerging adult demonstrates the ability to self-manage diabetes, meet with members of the diabetes healthcare team at recommended intervals, maintain glycaemic levels, and avoid acute complications [4]. Figure 70.1 provides a schematic of tasks during the period of transition and for the ultimate transfer between providers.

Problems with transition

Emerging adults with diabetes and their healthcare team encounter various issues during the transition from a specialized paediatric diabetes clinic to an adult endocrinology, diabetology, or primary care practice (Box 70.1). Notably, the topic of transition has continued to garner substantial interest from diabetes clinical and research communities for several reasons: first, there are more young people with type 1 diabetes and type 2 diabetes who need to undergo transition; and second, there is a deficiency of efficacious intervention research aimed at guiding the transition process and optimizing health outcomes of emerging adults with diabetes [57, 110–112].

One difficulty with transition is that the emerging adult must part with a long-term, familiar relationship with a group of paediatric healthcare professionals. In addition, there are fundamental differences in healthcare delivery between paediatric and adult settings [57]. Shulman et al. surveyed the Ontario Paediatric Diabetes Network regarding transition readiness and found that some paediatric providers perceived that adult diabetes clinics were less likely to have multidisciplinary holistic models of care, were less friendly to young adults, and had an infrastructure that made it more difficult to book appointments [113]. The longstanding relationship with the paediatric diabetes team had been family centred and

Box 70.1 Challenges for older teenagers and young adults with diabetes during the transitional period

- Diabetes self-care often loses priority to competing demands related to social, emotional, educational, and occupational interests and needs.
- Emerging adults with diabetes are at high risk for chronic hyperglycaemia.
- Mental health issues (i.e. depression, anxiety, disordered eating behaviours) are common at this age.
- Issues around sexual and reproductive health become paramount.
- Risk-taking behaviours around alcohol, smoking, and drug abuse typically increase in this age group.
- There is increased risk of acute complications (i.e. diabetic ketoacidosis and severe hypoglycaemia) for transitioning young adults.
- There is a risk of missing screening opportunities for eye and kidney complications and cardiovascular risk factor identification.
- Paediatrics and adult healthcare professionals employ different approaches to diabetes care.
- Loss to follow-up is a common problem at time of transition/transfer.
- Developing chronic diabetes complications may present in older adolescence and young adulthood and may go undetected and untreated.

holistic with respect to paediatric and adolescent developmental needs. Adult visits tend to be shorter in duration and tend to focus more on medical treatments [57]. Adult medical providers tend to focus the visit almost exclusively on the young adult rather than the family, with the belief that the individual is capable of making independent decisions regarding care and treatment [57]. Adult care providers often assume that the person with diabetes possesses the skills and capacity to perform diabetes care independently, which could be problematic if the emerging adult was ill-prepared by the paediatric team to assume the necessary responsibilities for their diabetes self-care. In turn, the emerging adult may feel unsupported and vulnerable following the transfer [109]. In some instances young adults may choose to reject adult care, limiting their openness to the medical provider's recommendations. These factors contribute to the frequent loss to follow-up care experienced by many emerging adults [57].

Indeed, more than one-third of older teenagers and emerging adults transferring care between paediatric and adult providers experience gaps in care exceeding six months [57]. Risk factors for gaps in care include a high number of stressful life circumstances, no college degree, and fewer than three paediatric diabetes visits in the year before transition [109, 114]. These gaps in care and loss to follow-up can lead to acute complications and the emergence of chronic complications that go undetected and untreated.

Unsuccessful transition is more likely to occur when emerging young adults lack skills for independent decision making, especially when they do not feel ready to handle such responsibilities [4, 57]. For example, a small sample of pre-transition teenagers with type 1 diabetes with an HbA_{1c} >9% (75 mmol/mol) reported a lack of formal preparation for transition, with a preference to defer being 'serious' about the transition process [115]. Furthermore, there are many age-appropriate social, emotional, educational, and work-related activities that compete for the attention of older teenagers and emerging adults, often superseding self-care and attendance at healthcare visits [109]. Many of these older teenagers and young adults may also feel uncomfortable disclosing their chronic medical condition to others, especially when entering a new school or work environment, making it challenging for those with diabetes to perform management tasks consistently [116]. The successful balance of diabetes self-care demands with these competing needs requires self-efficacy and self-advocacy. Transition preparation should include attention to these areas.

Gaps in care or loss to follow-up care results in elevated HbA_{1c} and glucose variability and places the emerging adult at increased risk for medical complications in both the short and long term [117]. The short-term complications are related to extreme glucose fluctuations (i.e. severe hypoglycaemia or hyperglycaemia) and can lead to emergency room use or hospitalization, especially in the absence of routine care. Further, persistent hyperglycaemia increases the risk for long-term microvascular and macrovascular complications [118]. Transition preparation from the paediatric team should include discussion of chronic diabetes complications, pregnancy planning, and routine screening for clinical evidence of early kidney and eye changes and risk factors for macrovascular complications. Otherwise, some emerging young adults may opt to avoid follow-up adult care rather than be suddenly faced with discussions regarding complications when they have been ill prepared [4].

There are several behavioural, psychosocial, and psychiatric challenges that can confront the older teenager and emerging adult with diabetes during the transition: these include diabetes distress, fear of hypoglycaemia, fear of hyperglycaemia, burnout, depressive symptoms, depression, anxiety, and disordered eating behaviours, among others. These challenges can interfere with effective self-care and consistent diabetes follow-up, leading to a vicious cycle of discouragement and burnout, which, in turn, may further diminish attention to diabetes self-care. Data in teenagers and emerging adults with type 1 diabetes identify psychosocial risk factors associated with reduced diabetes self-management and burnout [31, 114, 119, 120].

The coexistence of psychiatric conditions (Chapter 65), specifically depression and anxiety, brings considerable challenges to the management of diabetes during adolescence and emerging adulthood, having substantial impacts on self-care and consistent follow-up with medical providers [4]. Although such conditions are common in the general population, rates of depression and anxiety are higher in those with diabetes, especially during these developmental stages [121]. Collaborative care from professionals, including psychologists, social workers, and psychiatrists, versed in depression and anxiety disorders, including their impact on diabetes, is necessary to aid in the management of these conditions. Depressive symptoms and frank depression, associated with reduced motivation, often lead to reduced attention to diabetes self-care, yielding hyperglycaemia. For example, a study conducted in Singapore found an association between anxiety and depression before transition in both type 1 diabetes or type 2 diabetes and suboptimal glycaemic levels during follow-up visits [122].

Furthermore, the symptoms of depression and persistent hyperglycaemia can overlap with intensification of fatigue. Anxiety disorders also complicate living with and managing diabetes, in particular related to fear of needles or injections or fear of extremes of glucose levels. Fear of hypoglycaemia is more common than fear of hyperglycaemia, but some may fear the latter due to extreme concerns about the development of diabetes complications. Extreme anxiety can trigger panic attacks at times. Additionally, symptoms of hypoglycaemia and anxiety may overlap, further complicating management and generally leading to poor self-management [57].

Disordered eating behaviours and eating disorders, especially common in females, complicate diabetes management during the period of transition [57]. Cecilia-Costa et al. found that two of every five teenagers had moderate or high levels of disordered eating behaviour in their sample of 178 teenagers with type 1 diabetes [123]. A unique manifestation of eating disorders in diabetes is the purposeful restriction or omission of insulin. The deliberate underdosing of insulin serves as a very potent but dangerous weight loss strategy [124]. Many specific elements of type 1 diabetes and its treatment have been linked to the development of disordered eating behaviours and eating disorders, specifically the following:

- Initial loss of weight at the onset of the disease followed by weight gain on initiating insulin replacement.
- Occasional weight gain associated with intensive insulin therapy.
- Focus on diet as part of the diabetes treatment plan.
- The need to eat often without hunger, due either to peaking insulin action or hypoglycaemia [104, 125].

Factors associated with disordered eating behaviours include female sex, obesity, suboptimal glycaemic levels, presence of depressive symptoms, and executive dysfunction [123]. A recent publication also highlights associations between executive dysfunction and disordered eating behaviours in adolescents with type 1 diabetes; the former remains an area of ongoing investigation due to the importance of executive function in self-care in

type 1 diabetes [126]. Furthermore, disordered eating and eating disorders, particularly with insulin restriction or omission, can lead to deterioration in glycaemic levels and subsequent complications, even premature mortality [127–129]. It is crucial that teenagers and emerging adults with disordered eating behaviours or eating disorders receive specialized care, typically coordinated by the diabetes treatment team; however, this can be problematic if care for the affected person falls between the paediatric and adult healthcare systems [57].

In addition to the challenges already enumerated, there is a lack of empirically validated programmes to promote transition readiness, well-defined criteria to determine transition readiness, and methods to ensure a smooth transfer between paediatric and adult healthcare systems. Recently, questionnaires have been developed to assess transition readiness, such as Readiness Assessment of Emerging Adults with Type 1 Diabetes Diagnosed in Youth (READDY), Transition Readiness Assessment Questionnaire (TRAQ), and Readiness for Independent Self-Care Questionnaire-Adolescent (RISQ-T) and Parent (RISQ-P) [24, 130, 131].

Still, many older teenagers and young adults with diabetes experience gaps in care on transfer, deterioration of glycaemic levels, increased risk for acute complications, and the unrecognized emergence of chronic complications. Finally, there may be a component of reticence and even ambivalence regarding transition and transfer from paediatric providers. Many paediatric diabetes providers have known the individuals with diabetes for years and may have difficulty discharging them to adult providers, as they worry about how the individuals with diabetes will adjust to different models of care. Thus, there is a need for coordinated efforts between paediatric and adult providers to ease transition and transfer for individuals with diabetes and families as well as for the providers.

Existing transition programmes/interventions

Transition programmes do exist in the USA and other countries. However, there is no documented gold standard approach that has been empirically proven to yield optimal outcomes with respect to engagement, follow-up, medical outcomes, and psychosocial outcomes. The literature includes descriptions of structured and unstructured transition programmes, with structured programmes generally resulting in better outcomes. This section will describe published approaches to transition programmes along with suggestions for future directions.

There are three main approaches to developing transition programmes: clinics dedicated solely to emerging young adults, clinics focused on transition planning, and clinics that incorporate care coordination (care ambassadors or *diabetes navigators*) to ensure timely follow-up [4, 112]. In dedicated young adult clinics, there are specific days and times reserved for the care of young adults within the diabetes clinics. These focused clinics tend to be staffed by adult healthcare professionals who have a particular interest in the care of the emerging young adult.

Outcome results from care in young adult clinics have been variable, with some studies yielding no effect on glycaemic levels [132], while others have demonstrated superior outcomes with lower HbA_{1c} and reduction in hospital admissions [133, 134]. One study found high satisfaction levels in parents and young adults who participated in half-day transition clinics [135]. The differing results are likely to reflect the different designs and features of each of these programmes.

The second type of transition programme is related to transition preparation, which provides paediatric diabetes teams, individuals with diabetes, and families with a more structured and purposeful approach to transition planning aimed at creating a successful transfer. Cadario et al. retrospectively examined two groups who were transferred from paediatric to adult diabetes care in different ways [136]. The first group was sent a letter with information about their medical history and a scheduled appointment with an adult team. The second group participated in a structured transition programme, which included transition planning during the last year of paediatric care and discussions about what to expect following the transfer. Additionally, both paediatric and adult physicians participated in the last paediatric clinic appointment and first adult clinic appointment, with the paediatrician providing a medical summary to the adult doctor and the person with diabetes at the last paediatric appointment. Those in the second group showed more optimal outcomes, with a shorter time between last paediatric and first adult clinic appointments, better clinic attendance in the first year post-transfer, and improved HbA_{1c}. Furthermore, the second group reported satisfaction with the transition process [136]. More rigorous, prospective studies are needed.

The third type of transition programme utilizes a care coordinator who works closely with the older teenagers or young adults as they transition from paediatric to adult care. Van Walleghem et al. studied an intervention called the Maestro Project, which assigns a care coordinator to provide consistent contact and ensure access to diabetes care for the person with diabetes during the transition process [136]. In addition to care coordination, this programme offers a website, newsletter, meeting groups, and educational events. People with diabetes in this programme had greater retention in care, while the coordinator helped recapture individuals who had been previously lost to follow-up care. Other studies of care coordination have shown varied results; one demonstrated improved glycaemic levels and reduced hospitalizations [133], while another study comparing usual care with outreach by phone revealed no difference in outcomes [137]. Again, varying results may reflect differences in programme features or implementation.

Campbell et al. performed a systematic review of care transition among many chronic diseases of childhood, including type 1 diabetes, and compared the effectiveness of different interventions aimed at improving the transition of care for adolescents [112]. Four different interventions were reviewed: transition preparation training delivered in a two-day workshop, a web- and text message–based educational intervention, a one-hour one-on-one teaching session led by a nurse, and a comprehensive transition programme with a transition coordinator. Results indicated slight improvements in transition readiness, disease knowledge, and self-efficacy, especially in the technology-based intervention and with one-on-one teaching sessions. However, no major conclusions were drawn from the review, and it remains clear that there is a need for more prospective, longitudinal research [112].

In addition to these transition programmes housed within either paediatric or adult diabetes clinics, there may be opportunities to support older teenagers and young adults within a support group setting. Our team at the Joslin Diabetes Center in Boston examined the utility of monthly support groups for young adults with type 1 diabetes [116] and found that after five months of participation, self-reported diabetes burden had decreased and two-thirds of the participants had improved HbA_{1c}; there was a trend for improved self-care. Another report described a programme that combined aspects of many of those listed earlier, including transition planning,

coordinated transfer visits, an extended intake appointment with the adult diabetes staff, and group support sessions [138]. Those who participated in this programme had improved HbA_{1c}, decreased hypoglycaemic episodes, and greater diabetes-specific knowledge compared with those who received standard care. In addition, the Hemsley type 1 diabetes transition Let's Empower and Prepare (LEAP) programme provided pre-transition adolescents with type 1 diabetes with additional diabetes education, dietitian support, case managers, and the option of transferring to the young adult clinic and joining private social network groups. Compared with usual care, participation in the programme was associated with better glycaemic levels and psychosocial well-being [139]. Another multicentre RCT in Canada showed that young adults with type 1 diabetes who attended a transition programme with a transition coordinator showed an initial increase in clinic attendance, more satisfaction with care, and less diabetes-related distress than standard care [140].

Other innovative methods to help ease the transition process in youths with type 1 diabetes include using technology and group education. In a focus group for young people with type 1 diabetes in transition, the participants talked of a lack of communication technology during the transfer from paediatric to adult care [141]. Albanese-O'Neill et al. designed transition education for young adults with type 1 diabetes using group telehealth. Young adults with type 1 diabetes were recruited to attend five 30-minute videoconferences over eight weeks. Even though there was no statistically significant difference in diabetes self-efficacy or diabetes-related distress, they found that group videoconferencing was a feasible method to deliver diabetes education for young people with type 1 diabetes [142].

Other investigations are ongoing worldwide to design, implement, and evaluate transition programmes, given the increasing numbers of older teenagers and emerging adults with diabetes in need of improved systems of care and better health outcomes.

Conclusion

Significant physical, social, and emotional growth occurs during the adolescent years. The extra burden of diabetes adds further challenges at this time. Teenagers with diabetes have often developed a strong relationship with their paediatric diabetes care team, and the transfer to a new adult diabetes care team disrupts an established bond. Adolescents and young adults must develop increasing independence and responsibility for their diabetes care. This could be a time of crisis or a time of opportunity. By approaching this transition equipped with information about normal developmental stages and the unique challenges of diabetes self-care at this time, parents and diabetes healthcare providers can help older adolescents and young adults make this transition, empowering them to negotiate the transition and transfer as seamlessly as possible to preserve health and prevent the emergence of diabetes complications.

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71 Diabetes in Pregnancy

David R. McCance and Laura Cassidy
Regional Centre for Endocrinology and Diabetes, Royal Victoria Hospital, Belfast, Northern Ireland

Key points

- Pregnancy outcomes were transformed by the discovery of insulin in 1922 and the subsequent realization of the importance of optimal glycaemic management, close obstetric surveillance, and dedicated multidisciplinary care.
- The aim is to optimize blood glucose levels both before and during pregnancy through education and maternal empowerment, so that pregnancy may proceed as normally as possible and result in the birth of a normal baby at near term.
- Data registries indicate that congenital malformation and perinatal mortality rates remain 2–5-fold higher in pregnant women with diabetes than the background obstetric population.
- The benefits of pregnancy planning and pre-pregnancy care in improving outcomes are clear, but only a minority of women plan their pregnancy and education remains a key priority.
- Optimizing glycaemic levels is challenging for both the woman and clinician and must be balanced against the risks of hypoglycaemia.
- Randomized controlled trials suggest that insulin aspart and detemir are safe to use and have some benefits over conventional insulins; safety and efficacy data on very fast-acting analogues are awaited.
- Recent advances in insulin delivery and glucose sensing and their integration into hybrid closed-loop systems offer promise, but elucidation of their relative roles is urgently needed.
- Prevalence rates of type 2 diabetes, compounded by obesity, are being translated into pregnancy and now exceed type 1 diabetes in some populations, with similarly poor pregnancy outcomes.
- Consensus recommendations for the diagnosis of hyperglycaemia in pregnancy have generated a uniformity of approach, but individual variation remains across countries, and the risk, costs, and benefits of intervention are the subject of continued debate.
- Glycated haemoglobin (HbA_{1c}) or fasting plasma glucose (or other assessment of blood glucose) should be measured in early pregnancy to diagnose previously unrecognized type 2 diabetes and pre-diabetes and to identify women with severe hyperglycaemia.
- Metformin (in conjunction with dietary modification) is being used increasingly to supplement or replace insulin in the management of women with gestational diabetes mellitus (GDM) and type 2 diabetes, especially in those who are overweight; metformin crosses the placenta, and some international bodies still recommend insulin as first choice.
- Early postnatal visits in women with GDM are a unique opportunity to screen for and treat cardiometabolic risk factors, prevent or postpone the future risk of type 2 diabetes, and remind women of the need for contraception and future pregnancy planning.
- The adverse long-term implications of hyperglycaemia during pregnancy for both mother and offspring must be incorporated into cost-economic analyses.

The transformation of diabetic pregnancy outcomes following the discovery of insulin in 1922 was one of the outstanding medical success stories of the twentieth century [1]. Prior to insulin, these mothers 'gave birth astride a grave' [2] and the prospect of a viable fetus was negligible. By the middle of the last century, maternal mortality had declined significantly but the fetal outlook, even up to the early 1950s, remained very poor, with perinatal mortality rates of 20–25% [3]. During the next two decades pioneering work in centres including the Joslin Clinic in Boston, King's College Hospital in London, and Rigshospitalet in Copenhagen established the critical roles of optimal glycaemic management in mid to late pregnancy and of early delivery in reducing perinatal mortality [1, 3]. Along with this came increasing recognition of the need for multidisciplinary integrated care in units specializing in diabetic pregnancy [3]. In the 1980s, the advent of self-monitoring of blood glucose, glycated haemoglobin (HbA_{1c}), and insulin pen devices together with advances in obstetric surveillance helped to make pregnancy a more positive experience and further improved pregnancy outcomes. During recent decades, several randomized trials have offered new insight into the role of insulin analogues and oral anti-diabetes drugs in pregnancy.

Despite these advances, the goal of the Saint Vincent Declaration [4], that the outcome of diabetic pregnancy should approximate that of pregnancies of women without diabetes, has not been realized, and congenital malformation and perinatal mortality rates are still 2–5-fold higher than in the background obstetric population. Optimizing glycaemic levels remains challenging for both the woman and her physician, and efforts to intensify management must constantly be balanced against the risk of maternal hypoglycaemia. Despite these caveats, pregnancy outcomes for

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most women are successful and this undoubtedly reflects improved obstetric surveillance and better management of maternal hyperglycaemia. Recent advances in continuous subcutaneous insulin infusion (CSII), continuous glucose monitoring (CGM), and hybrid closed-loop systems have aroused considerable interest; however, their relative roles need to be elucidated, and it is uncertain what impact these devices will have on perinatal outcomes and overall patient satisfaction. The cost of this technology is likely to restrict its use to selected, educated, motivated women in experienced centres receiving dedicated supervision.

Over recent decades, the global pandemic of type 2 diabetes has been translated into pregnancy and now exceeds the proportion of women with type 1 diabetes in some populations, with similarly poor pregnancy outcomes. As the care of women with type 2 diabetes is predominantly community based, there is an urgent need to increase awareness among family doctors of the importance of contraception and pregnancy planning. Excessive maternal weight, a recognized factor for poor obstetric outcomes, frequently coexists with type 2 diabetes, and adds to the complexity of management.

While the association of overt diabetes during pregnancy with adverse pregnancy outcomes is clearly established, the relevance of minor degrees of hyperglycaemia to adverse outcomes has been surrounded by confusion and controversy. This situation eventually provided the catalyst for several landmark observational studies and randomized trials, which confirmed the continuum of risk and facilitated an international diagnostic consensus; however, variation still exists, and the glucose thresholds for diagnosis remain the subject of active debate. Recent follow-up studies showing independent associations of maternal hyperglycaemia with adverse metabolic and cardiovascular outcomes in the mother and offspring make a convincing case for early postnatal diabetes and cardiovascular risk screening, and such data must be included in cost-economic models of care.

Epidemiology

The seventh edition of the International Diabetes Federation (IDF) *Diabetes Atlas* estimated that 20.4 million or 15.8% of live births to women in 2019 had some form of diabetes in pregnancy [5]. Of these, 84% were due to gestational diabetes mellitus (GDM), 7.3% were the result of diabetes detected prior to pregnancy, and 8.5% were due to diabetes (including type 1 diabetes and type 2 diabetes) first detected in pregnancy. The vast majority of cases (87%) of hyperglycaemia in pregnancy are seen in low- and middle-income countries where access to antenatal care is often limited.

Between 1996 and 2010 the incidence of diabetes (GDM, type 1 diabetes, type 2 diabetes) during pregnancy doubled, affecting almost 1 in 10 pregnant women aged 30 years [6]. The numbers of pregnancies complicated by type 1 diabetes and type 2 diabetes increased by 33–44% and 90–111%, respectively, in Sweden and Scotland over a 15-year period since 1998 [7, 8].

A UK Confidential Enquiry into Maternal and Child Health (CEMACH, 2002–2003) of 3000 women with type 1 diabetes and type 2 diabetes in England, Wales, and Northern Ireland estimated the frequency of type 1 diabetes to be 1 in 364 (0.27%) and for type 2 diabetes 1 in 955 births (0.1%) [9]. A UK national report in England and Wales in 2015 estimated that approximately 1500 babies were born to women with type 1 diabetes, accounting for 0.21% of all live births [10].

The use of differing screening methods and diagnostic criteria both between and within countries makes comparative epidemiology difficult [11–13]. For example, within the UK the estimated crude prevalence of diabetes is 22.8% of live births, with an age-standardized prevalence of 19.9% (5.1% attributable to overt diabetes) [14]. By contrast, the prevalence estimated by the National Institute for Health and Care Excellence (NICE) in England and Wales using differing diagnostic thresholds was 5.0% (87.5% GDM, 7.5% type 1 diabetes, 5% type 2 diabetes) [15]. One retrospective study found a 30% increase in the incidence of GDM by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria compared with the 2015 NICE criteria [12]. The increase in GDM is compounded by obesity, which now affects about one in five women who give birth [16]. Despite the varying diagnostic criteria, there has been a progressive rise in the prevalence of GDM and overt diabetes during pregnancy over recent decades [17–19].

Physiology

Maternal metabolism adapts during pregnancy to ensure fetal growth and development. This involves a greater fall in plasma glucose and amino acids, and a greater rise in free fatty acids to overnight fasting than in the non-pregnant state (*accelerated starvation*). These changes are accompanied by hepatic insulin resistance, which ensures that maternal glucose is available to the fetus between meals [20].

Fasting glucose levels decrease from around 8 weeks' gestation and reach a nadir by the end of the first trimester due to insulin-independent glucose uptake by the fetus and placenta. From approximately 22 weeks' gestation, there is a progressive rise in post-prandial glucose and its associated insulin response, resulting from decreased insulin sensitivity, which parallels the growth of the fetal placental unit and rapidly reverses after delivery. In late pregnancy, maternal-to-fetal glucose transfer in the fasting state is also enhanced by maternal lipolysis, with free fatty acids becoming the main maternal fuel substrate. The inability of insulin to suppress lipolysis via inhibition of hormone-sensitive lipase in adipose tissue occurs at a time when maternal free fatty acid release and fatty acid oxidation are increased in parallel with reduced carbohydrate oxidation [21, 22]. The enhanced lipolysis [23] is attributed to the actions of human placental growth hormone and other placental hormones [24–27]. This *facilitated anabolism* brings about appropriate changes in carbohydrate, amino acid, and lipid metabolism and ensures adequate nutrients for the developing fetus.

The precise mechanism underlying the insulin resistance of late pregnancy is uncertain, but it appears to be related to a combination of increased hormone concentrations (human placental lactogen, progesterone, oestrogen, prolactin, and cortisol), increased free fatty acid concentrations, and changes to various cytokines elaborated by the placenta (tumour necrosis factor α, TNF-α), adipocyte fatty acid-binding protein, and leptin [28]. Maternal weight gain provides a source of calories for the fetus and mother, but increased visceral deposits contribute to insulin resistance.

Pathophysiology and its implications

To maintain glucose tolerance, maternal β cells compensate for the fall in insulin sensitivity by an approximate threefold increase of both the first- and second-phase insulin responses by the last

trimester [29], together with marked β-cell hypertrophy and hyperplasia [30].

Women who lack the necessary β-cell reserve, either absolutely as in type 1 diabetes or relatively as in type 2 diabetes or GDM, will have abnormal adaptation of carbohydrate, protein, and fat metabolism. Pregnant women with type 1 diabetes require sufficient insulin to compensate for increasing caloric needs, increasing adiposity, decreasing exercise, and increasing anti-insulin hormones. Insulin doses to maintain normoglycaemia and prevent maternal ketosis may increase up to threefold during pregnancy in type 1 diabetes. Women with type 2 diabetes will usually require insulin treatment in pregnancy, often at high doses, because of their obesity and physical inactivity. The increase in insulin resistance and requirements induced by the feto-placental unit reverses within a few hours of delivery, although requirements related to excessive maternal weight gain in pregnancy persist. An understanding of the underlying pathophysiological mechanisms is necessary for the successful clinical management of these women during pregnancy.

In GDM, the rise in glucose mostly results from a relative failure to increase insulin secretion in the face of chronic insulin resistance (primarily the result of obesity) that is accentuated in pregnancy and often compounded by excessive gestational weight gain. Women who develop GDM show decreased β-cell function [31, 32] similar to that of type 2 diabetes, and hence similar management strategies are appropriate.

The hypothesis that maternal hyperglycaemia accelerates fetal growth through provision of excessive glucose to the fetus at a time when the fetal pancreas can respond by increasing its production of insulin, an important fetal growth factor, was first proposed by Jorgen Petersen over 60 years ago [33]. Immunoreactive insulin is detectable in the human fetal pancreas by the seventh week after conception, with evidence of functional fetal β cells by the end of the first trimester [34]. The hypothesis is supported by animal and epidemiological data and has provided a basis for the concept of fetal programming. Other maternal fuels are likely to be implicated. More recently a *fetal glucose steal* phenomenon was suggested as an explanation for adverse neonatal outcomes despite seemingly satisfactory glycaemic levels in later pregnancy. This envisaged the early establishment of fetal hyperinsulinaemia, resulting in a lowering of fetal glycaemia, leading to an increased glucose concentration gradient across the placenta and hence glucose flux to the fetus. Such a hypothesis would have implications for pregnancy planning, and the need to optimize glucose levels in early pregnancy to prevent the establishment of fetal hyperinsulinaemia. An exaggerated glucose steal, by attenuating maternal glucose levels during an oral glucose tolerance test (OGTT), might provide an explanation for why some mothers with all the characteristics of diabetic fetopathy have *normal* glucose tolerance [35].

HbA_{1c} values tend to fall during normal pregnancy, possibly due to a combination of reduced fasting blood glucose levels and reduced red blood cell survival [36]. A small increase in late pregnancy may relate to developing iron-deficiency anaemia [37]. Alternative upper-limit reference ranges of 26 mmol/mol in the first and second trimesters and 40 mmol/mol in the third trimester have been suggested [38].

Classification

The World Health Organization (WHO) and IDF currently advise that hyperglycaemia in pregnancy can be classified as either GDM or diabetes in pregnancy [5, 39–42] (Table 71.1).

Table 71.1 Classification of diabetes in pregnancy.

Type of diabetes
Diabetes preceding pregnancy
• Type 1 diabetes
• Type 2 diabetes
Monogenic diabetes (e.g. *GCK*, *HNF1A*)
Secondary diabetes (e.g. cystic fibrosis)
Hyperglycaemia first detected in pregnancy
• Gestational diabetes
• Overt diabetes[a]

[a] Overt diabetes defined by oral glucose tolerance test (OGTT)/glycated haemoglobin (HbA_{1c}) criteria outside of pregnancy.
Source: Based on International Diabetes Federation 2019 [5], International Association of Diabetes and Pregnancy Study Groups Consensus Panel et al. 2010 [41], and World Health Organization 2013 [42].

GDM is diagnosed for the first time during pregnancy and may occur at any time during pregnancy, most commonly after 24 weeks [41]. Diabetes in pregnancy, which may occur at any time including the first trimester [40, 41], applies to pregnant women who have previously diagnosed diabetes, or have hyperglycaemia that was first diagnosed during pregnancy and meets WHO criteria for diabetes in the non-pregnant state. Most women with *overt diabetes in pregnancy* will have previously unrecognized type 2 diabetes (suggested by higher HbA_{1c} and features of the metabolic syndrome), but between 3% and 10% of those with newly recognized diabetes during pregnancy have type 1 diabetes. The diagnosis of type 1 diabetes may be suspected where the blood glucose levels are unusually high and in the absence of obesity. Some of these women may be able to stop insulin postnatally, even with apparent remission, but relapse typically occurs [43]. Serological tests for islet cell autoimmunity are usually strongly positive [44]. Approximately 75–90% of cases of hyperglycaemia in pregnancy are GDM.

A form of type 1 diabetes with rapid onset was first described in Japan in 1987, but subsequently reported in women from Southeast Asian countries [45]. The presentation is usually abrupt with severe diabetic ketoacidosis (DKA), often preceded by a short history of flu-like and abdominal symptoms. Investigations reveal raised serum pancreatic enzymes and hyperglycaemia, but normal HbA_{1c}, consistent with the acuteness of the presentation [45]. The condition most frequently occurs in late pregnancy or immediately postpartum, with high perinatal mortality rates [46].

Cystic fibrosis diabetes is now being encountered more often during pregnancy as survival into adulthood is common. Around one-third will have developed diabetes by the age of 20–30 years. In keeping with their longer life expectancy, the women are usually less ill with better pulmonary function, higher body mass index (BMI), and a lower prevalence of diabetes [47].

The diagnosis of monogenic diabetes may antecede pregnancy, but a small percentage of women initially considered to have type 1 diabetes or type 2 diabetes during pregnancy have genetic diabetes (most commonly *GCK* or *HNF1A* mutations or mitochondrial diabetes). Such a diagnosis is prompted by fasting hyperglycaemia but normal one- and two-hour values on OGTT screening among women with a normal BMI. Recognition is important given the risk of accelerated fetal growth depending on whether or not the mutation has been inherited [48].

Adverse pregnancy outcomes

Women with type 1 diabetes have a 2–5-fold increased risk of adverse pregnancy outcomes including congenital anomalies, stillbirth, and perinatal mortality [6, 7, 49–54]. A 2013 review of 12 population-based studies published within the previous 10 years comparing 14 099 women with type 1 diabetes with 4 035 373 women from the background population [52] reported as follows:

- Congenital malformations, 5.0% vs 2.1% (relative risk [RR] 2.4).
- Perinatal mortality, 2.7% vs 0.72% (RR 3.7).
- Preterm delivery, 25.2% vs 6.0% (RR 4.2).
- Large for gestational age (LGA) infants, 54.2% vs 10.0% (RR 4.5).

In the 2016 UK National Diabetes in Pregnancy Audit (NDIPA), almost one in two babies had complications related to maternal diabetes [53]. Outcomes are similar in mothers with type 2 diabetes [54–57].

Risk factors for mother and baby

Risk factors for poor pregnancy outcomes are well recognized, but modified by the type and duration of diabetes, glycaemic levels, and diabetes-related vascular complications [15]. These include:

- *General risk factors*: age, parity, weight, hypertension, smoking, and drug abuse.
- *Obstetric risk factors*: previous miscarriage, multiple pregnancy, nutritional deficiency, late booking, and poor obstetric history.
- *Maternal risk*: miscarriage, accelerated retinopathy and nephropathy, hypoglycaemia and hypoglycaemic unawareness, DKA, pre-eclampsia, hydramnios, operative delivery, and infection.
- *Fetal risk*: stillbirth, perinatal mortality, congenital anomalies, Small for Gestational AGE (SGA), Large for Gestational Age (LGA), preterm delivery, operative delivery, shoulder dystocia and birth injury, neonatal hypoglycaemia, polycythaemia, hypocalcaemia, and respiratory distress syndrome.

Rationale for pregnancy planning

Optimizing glycaemic levels before pregnancy and early during the first trimester is associated with improved outcomes, reduced congenital anomalies, and lower perinatal mortality [15, 58–60]. A meta-analysis [59] reported that implementation of pre-pregnancy care is associated with an RR of 0.25 (95% confidence interval [CI] 0.16 to 0.37) and number needed to treat (NNT) of 19 (95% CI 14 to 24), for congenital malformations, and an RR of 0.34 (95% CI 0.15 to 0.75) and NNT of 46 (95% CI 28 to 115) for perinatal mortality. It is important for the woman to realize that these benefits occur with any improvement in HbA_{1c} [61, 62], but the average reduction in HbA_{1c} of 13 mmol/l (1.2%) was achieved at the expense of an increased risk of hypoglycaemia during the first trimester (RR 1.51; 95% CI 1.15 to 1.99) [59].

There is a critical need for the healthcare professionals to embrace every opportunity to educate women and adolescents of reproductive age about the risks of unplanned pregnancies and the improved outcomes resulting from pregnancy planning [60, 63, 64], including cost benefits [65].

Components of a prepregnancy service

There are two separate components to reproductive health education for women with type 1 diabetes: preconception counselling and prepregnancy care [63].

Preconception counselling is the education of, and discussion with, women of reproductive age about pregnancy and contraception. Beginning at the onset of puberty or at diagnosis, and utilizing appropriately customized resources [66], it should take place at regular intervals during a woman's reproductive years and include education and discussion on the following:

- The use of contraception and assessment of risks for each method until a woman is prepared and ready to become pregnant [15, 60, 63].
- Increased risks of adverse outcomes associated with hyperglycaemia.
- Nature of preconception care and how it can improve pregnancy outcomes.
- Risks of smoking and alcohol consumption during pregnancy.
- Avoidance of statins and renin–angiotensin system (RAS) inhibitors during early pregnancy [15, 60].

Prepregnancy care is the additional care required to prepare a woman with diabetes for pregnancy [15, 60, 63, 67]. Ideally, this should be delivered by a multidisciplinary team, who will care for her during pregnancy, and should begin at least six months before conception. The aim is to optimize glycaemic management before conception (Table 71.2).

Challenges associated with prepregnancy care

Prepregnancy care recommendations and, particularly, glycaemic targets are demanding and many women are unable to achieve them. Despite the clear advantages of prepregnancy and coordinated pregnancy care in improving outcomes [68, 69], not all women with type 1 diabetes attend. Such women are more likely to be younger, with no third-level education, and not married or in a relationship [70]. Awareness of the rationale for prepregnancy care in women with type 1 diabetes has increased in recent years, even among non-attenders. In one study, the commonest reason for not attending was a pregnancy that was not fully planned or conception occurring more quickly than expected (45%). Other reasons for non-attendance were fertility concerns (31%), negative relationships with healthcare professionals (21%), complex emotional issues (17%) including fear of being disappointed and wanting a normal pregnancy, and logistical or financial concerns (10%) [71].

Behaviour patterns frequently coexist and so women with sub-optimally managed diabetes are also more likely not to use regular contraception, to have unplanned pregnancies, to smoke cigarettes, to present late to pregnancy clinics, and to have more diabetes complications [9, 68, 72]. Consequently, those women who would probably benefit most from rigorous pregnancy counselling are least likely to receive it, and this may be one of the greatest challenges.

Adverse fetal outcomes

Congenital malformations

Recognition of the increase in congenital malformations in infants of women with diabetes dates back to observational studies in the 1960s [73], when odds ratios (OR) of up to 7.9 were reported;

Table 71.2 Aims of prepregnancy care for women with diabetes.

Contraception
Document use of effective contraception
Continue contraception until optimum glycated haemoglobin (HbA_{1c}) achieved
Optimize glucose levels
Aim for HbA_{1c} as close to normal range as possible without significant hypoglycaemia
Advise blood glucose monitoring before and 1 h post-prandial, and occasionally during the night:
• Pre-meal glucose <5.3 mmol/l
• Post-meal glucose (1 h) <7.8 mmol/l
Stop oral anti-diabetes agents and initiate insulin if suboptimal glucose levels
Consider metformin if improved glycaemia outweighs potential risks
Advise on management of hypoglycaemia
Diet, exercise, and structured education
Refer to dietitian for education on regular basis
Advise small to moderate portions of low glycaemic index carbohydrates
Education about weight loss if body mass index (BMI) ≥27 kg/m^2
Encourage regular exercise
Provide smoking and alcohol cessation advice
Prescribe folic acid supplements
Supplemental dose: 5 mg/d (dose may vary)
Review other medications
Stop angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists, statins, and diuretics
Treat hypertension with methyldopa or labetalol
Screen for diabetes-related complications
Assess for retinopathy at initial visit (if not assessed in previous 6 mo) and then annually. If retinopathy is present, consider referral to ophthalmologist
If proteinuria or reduced glomerular filtration rate (GFR) is present, refer to nephrologist
Assess cardiac status and consider referral to cardiologist.
Screen for rubella immunity
Counsel on risks of pregnancy with diabetes and obesity
To fetus: miscarriage, malformation, stillbirth, neonatal death, macrosomia
To pregnancy: eclampsia, premature delivery, caesarean delivery
Progression of diabetes-related complications
Consider referral to obstetrician or diabetes specialist midwife
Assessment of obstetric risk
Further education and support

congenital malformations were quickly linked with maternal periconceptional hyperglycaemia [58, 59, 74–77]. The relationship was further defined by the advent of HbA_{1c} measurement, which forms the basis of current recommendations [62, 63]. The absolute risk rises from approximately 3% when the periconceptional HbA_{1c} is 50 mmol/mol to 10% when it is 100 mmol/mol, although with wide confidence intervals limiting the certainty of prediction (Figure 71.1) [62].

Since the 1990s, the rates have been 1.6–2.7 times higher than background [49, 56, 78, 79] with no apparent improvement over time with the exception of a Canadian study [6], which reported a 23% reduction in relative risk from 1996 to 2010. More recently, registry data have reported similar malformation rates in women with type 2 diabetes to type 1 diabetes (RR 1.19), even when first-trimester HbA_{1c} were lower [9, 56, 57, 60, 62, 74].

The most frequent anomalies in offspring of women with diabetes are cardiac defects (3–4-fold higher), followed by neural tube, musculoskeletal, and genitourinary defects [49]. Multiple anomalies are present in up to 20% of malformed infants (RR up to 12) [9, 49]. Caudal regression is rare, but relatively specific to diabetic pregnancy [80] (RR 26). The relative risk for heart and central nervous system defects is about twofold higher, although with some exceptions.

Most abnormalities occur in the teratologically sensitive period till the seventh gestational week, adding to the importance, and challenge, of family planning and preconception management. It is hypothesized that tissue-specific developmental control genes are regulated at specific times in embryonic development by glucose metabolism, or that maternal diabetes, possibly through epigenetic changes, reduces the precision of gene regulation [81].

Increased BMI is positively associated with congenital malformations in the general population. A meta-analysis showed a significant dose–response relationship between BMI and neural tube defects (OR 1.20 for overweight and 1.87 for obesity) [82], and similarly for congenital heart defects (OR 1.08 for overweight; 1.23 for obesity, 1.39 for severe obesity) [82, 83].

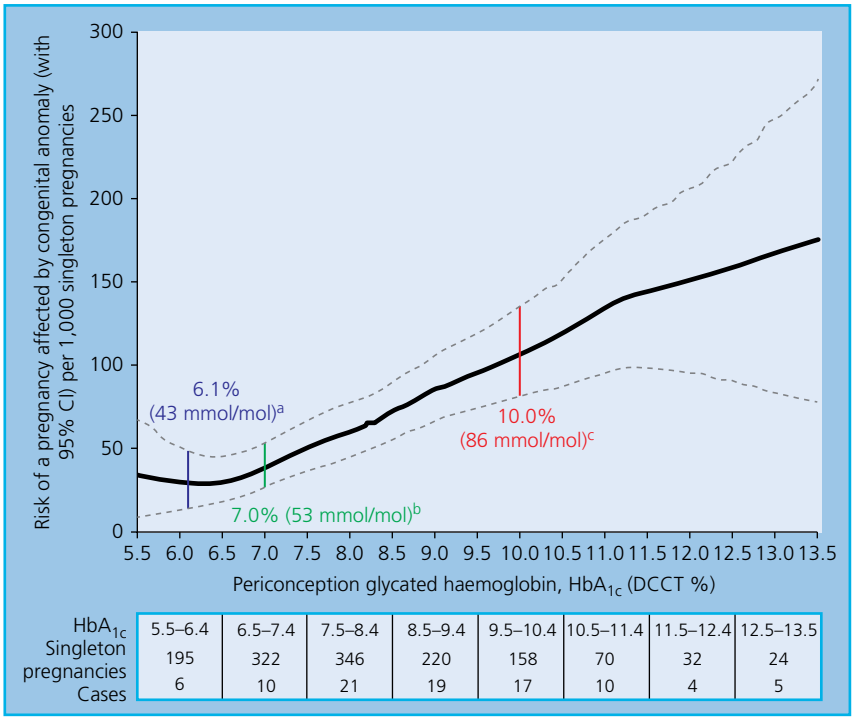
Folic acid supplementation in the periconception period prevents the occurrence of neural tube defects (overall RR 0.28) and a preventive effect on other congenital malformations has been suggested but not confirmed [84]. Guidelines recommend periconceptional supplementation with folic acid of at least 400 μg daily [60] or higher doses of 4–5 mg daily [15, 60].

Miscarriage

Fertility is usually normal in women with type 1 diabetes, although delayed menarche in girls diagnosed before puberty is common, especially if glycaemic management is suboptimal [85]. Miscarriage rates among women with diabetes appear to be similar to those in the general population (12–15%), although the risk is increased 3–4-fold when hyperglycaemia occurs in early pregnancy [86] and may relate to non-viable congenital malformations. Maternal obesity is associated with reduced success with *in vitro* fertilization and may be a risk factor for first-trimester miscarriage [87].

Stillbirth

Antenatal death *in utero* (defined as fetal loss after 24 completed weeks' gestation) remains the most feared of all outcomes for women with type 1 diabetes and their clinicians. In the UK CEMACH study, the rate was 4.7-fold greater than the general antenatal population (5.7/1000 births) and similar in type 1 diabetes (25.8/1000) and type 2 diabetes (29.2/1000 births) [9]. A population-based study in 2013 reported the risk to be approximately three times higher that of the background population, affecting 1 in 100 pregnancies in the UK between 2009 and 2011 [88], with little change over the previous 10 years [9, 10]. Fetal death is likely to be multifactorial [89] and includes congenital anomalies, chromosomal abnormalities, infection, placental vascular problems (associated with an increased risk of pre-eclampsia and renal and macrovascular disease), cigarette smoking (up to 19% of women in one study) [90], and third-trimester maternal hyperglycaemia [61, 91]. Increased maternal age and significantly raised BMI are also risk factors for stillbirth, both with and without diabetes, and may explain comparable rates in type 1 diabetes and type 2 diabetes [57, 92]. Compared with normal fetuses, macrosomic fetuses (birth weight above the 90th centile) with increased oxygen requirement [93], mild acidaemia, and borderline placental vascular supply may be particularly at risk. Approximately one-quarter of stillbirths are unexplained [94]. A systematic review of four studies of adverse pregnancy outcome in type 1 diabetes and type 2 diabetes found increased perinatal mortality associated with



HbA_{1c}	5.5–6.4	6.5–7.4	7.5–8.4	8.5–9.4	9.5–10.4	10.5–11.4	11.5–12.4	12.5–13.5
Singleton pregnancies	195	322	346	220	158	70	32	24
Cases	6	10	21	19	17	10	4	5

Figure 71.1 Association between periconception glycated haemoglobin (HbA_{1c}) in women with pre-existing diabetes and the risk (with 95% confidence intervals [CI]) of a pregnancy affected by major congenital anomaly. To convert values from HbA_{1c} in % into mmol/mol, subtract 2.15 and multiply by 10.929. DCCT, Diabetes Control and Complications Trial. Source: Data from Bell et al. 2012 [62].

hyperglycaemia (pooled OR 3.23; 95% CI 1.87 to 4.92 [95], although the studies had methodological limitations.

Marked oscillations in maternal glycaemic levels may explain the accelerated fetal growth and fetal compromise seen in some pregnancies with apparently excellent diabetes management [96]. When fetal death occurs it is usually after 32 weeks [9, 10, 92, 97] and frequently in the context of hyperglycaemia, polyhydramnios, and/or accelerated fetal growth [98]. By contrast, women with diabetes and vasculopathy and/or pre-eclampsia may develop intrauterine growth restriction (IUGR), and fetal demise, as early as the second trimester, probably related to placental vascular disease. Amniotic erythropoietin, a marker of chronic fetal hypoxia in late pregnancy, is higher in diabetic than non-diabetic pregnancies, and in one study of women with type 1 diabetes correlated inversely with cord blood pH and partial pressure of oxygen (pO_2) at birth [93].

Current recommendations to deliver women from 37 + 0 weeks' gestation, or even earlier if there are specific maternal or fetal risks [15], reflect this concern, but studies have shown that the risk of stillbirth in offspring of women with pre-existing diabetes occurs from as early as 32 weeks' gestation [92].

Accelerated fetal growth

The intrauterine diabetic milieu promotes an excess of body fat, an increase in muscle mass, and organomegaly, particularly liver and heart, without increased brain size. The excess fat is rapidly lost and by 6 months of age these babies are indistinguishable from babies of mothers without diabetes.

Birth weight, although routinely and almost universally measured at birth, is a crude estimate of fetal growth, as short–fat and long–thin newborns may have similar weights, but different *in utero* exposures and neonatal risks. Various definitions of accelerated fetal growth are used, including birth weight over 4000 g or 4500 g, or birth weight over the 90th centile or two standard deviations above the mean weight for gestational age and sex. The latter measure is preferred, as it allows identification of premature newborns with excessive fetal growth, but even this does not characterize the selective organomegaly seen in the infants of women with diabetes. Accelerated growth can be detected on routine fetal abdominal circumference ultrasound measurement at 28 weeks' gestation [99]. Although characteristic, this finding is not specific, as it can result from maternal obesity and excess gestational weight gain. Fetal liver length measurements may be more specific to hyperglycaemia, but are technically challenging [100].

The UK CEMACH survey reported that 21% of singleton babies of women with diabetes weighed over 4000 g compared with 11% in the general population [9]. Other studies have reported babies of mothers with diabetes to be 1.8–5.2 times more likely to be above the 90th centile compared with the background population [9, 49, 52, 101], with 49–63% being LGA and 20–25% having a birth weight more than 4000 g [49, 50, 102], with similar rates in type 2 diabetes. The rate of macrosomia was 52% in the recent UK cohort [57]. Maternal obesity (increasing in women with type 1 diabetes) and gestational weight gain may contribute to these persistently high rates of fetal overgrowth [103].

Growth acceleration may start as early as 18 weeks' gestation [104]; however, growth potential of fetuses seems to be determined by prevailing maternal glycaemia before then, and excessive growth can continue despite optimal glycaemic levels in later pregnancy [105]. Higher maternal age, height, parity, BMI, presence of diabetes, gestational age at delivery, and male fetal sex are all significantly related to macrosomia [106]. Other factors include placental size, uterine blood flow, hypertension, and cigarette smoking.

The influence of genetic factors on fetal growth patterns is illustrated by the variable effects of *GCK* and *HNF4A* mutations depending on whether the mother and fetus have inherited the mutation (Chapter 20) [48, 107–109]. Certain mutations and polymorphisms have also been identified in genome-wide association studies [110].

The clinical significance of macrosomia pertains to the risk of complications presented by delivery of a large infant, such as shoulder dystocia, obstructed labour, perinatal hypoxia–ischaemia, and birth injury (e.g. brachial plexus injury and fractured clavicle or humerus) [9, 111].

Shoulder dystocia

Shoulder dystocia occurs when the baby's anterior shoulder becomes lodged behind the mother's pubic bone following delivery of the head. Precise definitions differ and are variously based on the time delay between delivery of the head and shoulders (e.g. one minute), or where excessive downward traction or special manoeuvres are needed to deliver the shoulders.

The reported rates of shoulder dystocia in women with pre-existing diabetes in the UK are 7.9% (over twice the rate in the general population) and are directly related to birth weight (<1% for birth weight <2.5 kg vs 43% for birth weight >4.5 kg) [9]. Brachial plexus injury (Erb's palsy) of 4.5/1000 births is infrequent, but occurs at 10 times the rate of the general population, while the fracture rates (usually of the clavicle and humerus) is 7/1000 births [9]. Another study of women with type 1 diabetes [112] reported an incidence of Erb's palsy of 2%. Although most babies with brachial plexus injuries recover with no long-term sequelae, the most serious damage occurs in the largest babies [113]. Given the high rate of preterm delivery and caesarean section in this cohort, the complication rate would likely be even higher if there were more normal deliveries at term. SGA infants of women with diabetes appear to be at even greater risk of adverse outcome, especially of neurodevelopmental sequelae, often compounded by preterm delivery. Delivery must be planned at an appropriate unit, as specialist neonatal care is likely to be required.

Neonatal hypoglycaemia

Neonatal hypoglycaemia, if severe and prolonged, can cause brain injury, poor neurodevelopmental outcome, and even threaten survival [114]. Infants at risk include those born to a mother with diabetes, those SGA or LGA, and late preterm deliveries [115]. Glucose is the principal energy substrate for the fetus, with fetal blood glucose levels typically corresponding to 60–80% of maternal levels [116]. Neonatal hypoglycaemia is attributed to fetal hyperinsulinaemia, which occurs in response to maternal (and subsequently fetal) hyperglycaemia during pregnancy.

Rates of neonatal hypoglycaemia vary depending on the definition of hypoglycaemia, maternal diabetes type, antenatal glycaemic levels, and infant birth weight [117]. In general, 30–50% of infants born to mothers with diabetes will have hypoglycaemia during routine testing in the postnatal period [118, 119]. The definition of neonatal hypoglycaemia is difficult, as glucose levels can fall to below 2.0 mmol/l in the first two hours of life in healthy babies [120, 121]. Even in the absence of food intake, blood glucose rises during in the first three hours of life, so earlier monitoring is not informative. Blood glucose monitoring should be done before the feed to detect a nadir in blood glucose level.

Pathological hypoglycaemia is persistent hypoglycaemia beyond the first few hours of life. Although there is no consensus on the numerical value, guidelines recommend screening of at-risk infants and maintaining blood glucose at ≥2.6 mmol/l (47 mg/dl) [115].

If neonatal hypoglycaemia is suspected, the plasma or blood glucose concentration should be determined by using a laboratory enzymatic method, such as glucose oxidase, hexokinase, or the dehydrogenase method [115], as capillary blood glucose readings have poor precision at low values.

The main objective of glycaemic management during labour is to avoid maternal hyperglycaemia and minimize the risk of neonatal hypoglycaemia and fetal acidaemia [122]. Maintenance of maternal blood glucose between 4 and 8 mmol/l during labour and delivery [15] appears optimal. Delivery results in an abrupt cessation of maternal glucose supply to the infant, which in the setting of hyperinsulinaemia will result in hypoglycaemia.

Most cases of neonatal hypoglycaemia occur in the first 24–48 hours after delivery [115, 118] and last a maximum of a few days. Therefore, if a baby is clinically stable, and has no evidence of clinically significant hypoglycaemia, blood glucose monitoring may be discontinued when laboratory-measured glucose levels are persistently above 2.0 mmol/l. Ideally, breastfeeding should start immediately after delivery and be offered every 3–4 hours, or more frequently if the baby demands. In the absence of clinical signs, NICE guidelines [15] recommend that two consecutive (usually 2–4 hours apart) blood glucose levels below 2.0 mmol/l, at least 3–4 hours after delivery, that cannot be raised by oral or tube feeding require intervention, aiming to raise the blood glucose level to >2.5 mmol/l [15, 121]. Management of hypoglycaemia with abnormal clinical signs, for instance reduced level of consciousness or convulsions, is a medical emergency necessitating full clinical evaluation and transfer to the neonatal intensive care unit (NICU). Intravenous glucose (10% dextrose) must be given immediately starting at 5 mg/kg/min (equivalent to 3 ml/kg/h) and an increase may be needed as indicated by frequent blood glucose monitoring. Intramuscular glucagon (200 µg/kg) is useful if there are clinical signs and a delay in achieving intravenous access; glycogen will be broken down to release glucose, but the effect is transient, lasting less than one hour.

Other neonatal complications

Infants of mothers with diabetes commonly have a raised haematocrit, possibly due to fetal hyperinsulinaemia and chronic tissue hypoxia [123], but not strongly related to birth weight or late maternal HbA_{1c} [124]. Values are lower in babies born by caesarean section. Offspring are at increased risk of respiratory distress syndrome [125], most likely related to prematurity and delivery by caesarean section (recognized risk factors for respiratory morbidity) [126]. Jaundice is more common in babies who are LGA and is likely to be multifactorial in origin, including birth trauma, erythrocytosis, haemolysis, and immature hepatic bilirubin conjugation. Transient hypertrophic cardiomyopathy is characterized by ventricular septal hypertrophy that obstructs the left ventricular outflow tract and occurs in 30–80% of babies of mothers with diabetes [127]. It may be sufficiently severe to present with congestive cardiac failure and can cause fetal or neonatal death, but usually has a benign course, resolving with one month without any clinical sequelae. Transient neonatal hypocalcaemia, possibly related to glycaemia and less frequently hypomagnesaemia, can occur, but is rarely of clinical significance unless the baby has other complications, such as perinatal hypoxia–ischaemia, and routine screening is not required.

Maternal diabetes complications

Maternal hypoglycaemia

Hypoglycaemia is defined as a blood glucose level <4.0 mmol/l (70 mg/dl) and is an almost inevitable consequence of trying to achieve near-normal maternal blood glucose levels. In one study of 108 women with type 1 diabetes, 45% experienced severe hypoglycaemia during pregnancy, which was 3–5 times more frequent in

early pregnancy compared with immediately prepregnancy [128]. Predictors of severe hypoglycaemia, requiring external assistance, include impaired hypoglycaemia awareness, a past history of severe hypoglycaemia, long duration of diabetes, low HbA_{1c} in early pregnancy, fluctuating glucose levels, and excessive use of supplementary insulin between meals [128–130]. Impaired hypoglycaemia unawareness, which appears to result from the loss of the counter-regulatory response to hypoglycaemia, is accentuated in pregnant women with diabetes [131] and presents an additional clinical challenge.

The UK CEMACH study reported that 61% of women with type 1 diabetes had recurrent hypoglycaemic episodes during pregnancy and 25% had severe hypoglycaemia [9]. Moreover, 21% of women with type 2 diabetes also had recurrent episodes of severe hypoglycaemia, but neither recurrent nor severe hypoglycaemia was associated with poor pregnancy outcome (OR 1.1; 95% CI 0.7 to 1.7 and OR 1.3; 95% CI 0.7 to 2.3, respectively). Follow-up studies have shown no apparent long-term consequences of maternal hypoglycaemia on the offspring up to 5 years of age [132].

The major risk of hypoglycaemia seems to be to the mother and includes loss of consciousness, seizures, hospital admission, and death [50, 132, 133]. One study suggested that this risk can be reduced by a focused intervention including education of caregivers and women [134].

Diabetic ketoacidosis

Historically, DKA prevalence rates of 1–2% during pregnancy were reported [135, 136], and recent evidence suggests that these have not diminished (2.7% in the 2016 UK NDIPA [10]). Although DKA is typically associated with type 1 diabetes, it also occurs in women with type 2 diabetes and has been reported in GDM. It is important to note that glucose levels at presentation are often lower than anticipated due to utilization of maternal glucose by the fetus and placenta [137, 138], and therefore the possibility of DKA should be considered in women with all types of diabetes who present unwell during pregnancy, even if blood glucose is normal or low.

DKA occurs in the setting of absolute or relative insulin deficiency. Insulin deficiency leads to hyperglycaemia and a rise in plasma glucagon, which in turn stimulates hepatic gluconeogenesis and lipolysis, with subsequent ketogenesis. The physiological changes that occur during pregnancy can increase the risk of ketosis and subsequent acidosis, although the precise factors that are most detrimental to the fetus remain poorly understood [139].

Protocols for the rapid diagnosis of DKA in pregnant women are similar to those in non-pregnant women, although care is needed to avoid overhydration. Precipitants such as infection, systemic illness, hyperemesis, dehydration, insulin omission, and medications (e.g. tocolytics and corticosteroids) need to be urgently identified and treated. Particular vigilance is required for the effects of vomiting and starvation arising as a result of hyperemesis, gastroparesis, eating disorders, and gastroenteritis.

Fetal mortality rates of 9–35% have been reported in studies over the last 20 years, although current rates are likely to be lower [140]. The worst outcomes occur when diagnosis and treatment are delayed [135, 136]. Women with type 1 diabetes should be prescribed ketone strips and receive education on DKA prevention and detection as part of the sick-day rules.

Retinopathy

Pregnancy is a risk factor for progression of diabetic retinopathy [141], although these changes often regress postpartum without increased long-term risk [142]. The mechanism of retinopathy progression is unknown, although multiple theories exist related to hormonal, haemodynamic, metabolic, and immunological changes during pregnancy. The risk of progression of retinopathy during pregnancy is greatest in women with moderate to severe retinopathy who enter pregnancy with hyperglycaemia and experience a rapid improvement in their glucose levels during the first trimester. In a prospective cohort study of 155 women with diabetes [143], retinopathy developed in 10.3% of those with no retinopathy, 21.1% with microaneurysms only, 18.8% with mild non-proliferative retinopathy, and 54.8% with moderate to severe non-proliferative retinopathy at baseline. Proliferative retinopathy developed in 6.3% of women with mild and 29% with moderate to severe baseline retinopathy. The risk of progression to sight-threatening retinopathy is approximately 20–30% for those with moderate to severe retinopathy before pregnancy, but ≤2% for those with minimal disease or no retinopathy.

In the Diabetes Control and Complications Trial (DCCT), 80% of participants with a fall in HbA_{1c} of ≥35 mmol/mol (3.2%) during pregnancy had some deterioration, compared with no overall change in retinopathy when the HbA_{1c} fall was ≤17 mmol/mol (1.6%) [142]. The benefits of improved glycaemia to the fetus, however, outweigh any risk to the mother, and women with no or minimal retinopathy at baseline are at minimal risk.

The common practice of instituting tight glycaemic management at the onset of pregnancy confounds our ability to conclude that pregnancy *per se* is the cause of retinopathy, because rapid tightening of glycaemia levels has been associated with an acute deterioration in retinopathy outside pregnancy [144, 145]. Diabetic retinopathy may be associated with diabetic nephropathy and hypertension, with the latter being reported as a risk factor for progression and thus meriting careful monitoring and treatment during pregnancy [146]. Hormonal changes are also suspected of exacerbating retinopathy. For example, the characteristic progesterone surge of pregnancy with upregulation of intraocular vascular endothelial growth factor (VEGF) [147], together with other placental hormones such as placental growth factor (PGF; the concentrations of which increase 15–20-fold between 8 and 32 weeks' gestation), may contribute to increased retinal capillary leakage and neovascularization [148]. PGF appears to regulate maternal insulin-like growth factor I (IGF-I), which in turn may promote retinal neovascularization by supporting VEGF induction of endothelial cell proliferation [149]. Other possible mechanisms for retinopathy progression include increased blood volume and cardiac output resulting in a hyperdynamic retinal capillary blood flow, and inflammation resulting in retinal vascular dysfunction from leucocyte adhesion to the retinal vasculature [150, 151].

The risk of retinopathy progression during pregnancy continues into the postpartum period [152], requiring ongoing monitoring; however, pregnancy does not generally alter the natural course of diabetic retinopathy [142] and baseline retinopathy status would seem to the most important independent factor for progression [153].

Hypertension

Hypertension complicates 10% of pregnancies in women without diabetes [154], while up to 40% of women with diabetes are reported to have a blood pressure exceeding 140/90 mmHg during pregnancy [155]. The combination of hypertension and diabetes results in a higher number of adverse maternal fetal outcomes than either alone [156].

In type 1 diabetes, additional risk factors for hypertensive disorders of pregnancy include diabetes duration, high HbA_{1c} and diabetic

nephropathy, or early-pregnancy proteinuria [157–159]. The impact is generally less among pregnant women with type 2 diabetes due to lower rates of pre-eclampsia, although fewer studies have been reported [160]. Compared with type 1 diabetes, pregnant women with type 2 diabetes tend to be older, have more obesity (resulting in more chronic/essential hypertension), with shorter duration of diabetes and greater multiparity. Proteinuria is more common in type 2 diabetes, but is less predictive of pre-eclampsia [160]. Obesity is also a significant risk factor for pre-eclampsia (including severe pre-eclampsia), and may help explain the increasing levels of blood pressure in pregnancy in recent decades [161].

There are four hypertensive disorders (defined by severity, time of onset, and associated features) as detailed in Table 71.3 that can occur during pregnancy, all of which are more common in women with diabetes and increase the risk of adverse pregnancy outcomes.

Table 71.3 Classification of hypertensive disorders of pregnancy.

Chronic hypertension	Blood pressure (BP) ≥140 mm/Hg or ≥90 mmHg prior to pregnancy or before 20 weeks' gestation; or hypertension diagnosed for the first time during pregnancy without resolution postpartum. In women with diabetes, some centres regard BP >135/85 mmHg or even >130/80 mmHg as an indication for treatment [60, 155]
Gestational hypertension	BP ≥140 mmHg systolic or ≥90 mmHg diastolic first detected after 20 weeks' gestation without proteinuria or other features of pre-eclampsia Retrospective diagnosis of transient hypertension is made if BP returns to normal by 12 weeks postpartum, while diagnosis of chronic hypertension if raised BP persists [162]
Pre-eclampsia	BP ≥140 mm/Hg systolic or ≥90 mmHg diastolic and proteinuria (≥1+ on a sterile urine dipstick or ≥300 mg/24 h) after 20 weeks' gestation [154]; pre-eclampsia may further be classified into early-onset (<34 weeks' gestation) and late-onset pre-eclampsia (≥34 weeks' gestation) Severe pre-eclampsia is defined by any one of: • Severe hypertension (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg, or both) • Cerebral or visual disturbance • Epigastric or right upper quadrant pain • Oliguria • Pulmonary oedema • Cyanosis • Impaired liver function • Thrombocytopaenia • Intrauterine growth restriction Eclampsia is defined as new-onset grand mal seizures in women with pre-eclampsia; some women do not have diagnosed pre-eclampsia and some may present with eclampsia in the postpartum period
Chronic hypertension with superimposed pre-eclampsia	Women with hypertension in early pregnancy developing new-onset proteinuria (as detailed above) In women with diabetic nephropathy and proteinuria in early pregnancy, the development of pre-eclampsia is defined by a sudden increase (≥15%) in systolic or diastolic blood pressure, or a sudden 2–3-fold increase in proteinuria and/or thrombocytopaenia (platelets <100 000), and/or an increase in aspartate aminotransferase or alanine aminotransferase

The greatest risk is with early-onset pre-eclampsia and the lowest with gestational hypertension.

Chronic hypertension is associated with an increased risk of fetal loss, superimposed pre-eclampsia, preterm birth, intrauterine fetal growth restriction, and neonatal morbidity [163]. In addition, women with chronic hypertension are at risk of developing severe hypertension (≥160/110 mmHg), pre-eclampsia, and stroke during pregnancy. In mild cases, gestational hypertension is not associated with pregnancy complications; however, progression to pre-eclampsia (10–50%) or to severe hypertension (≥160/110 mmHg) occurs, with a comparable risk of severe pregnancy complications as in women with pre-eclampsia [163]. The diagnosis of pre-eclampsia is problematic in women with pre-existing microalbuminuria or nephropathy, and may alternatively be defined by worsening hypertension and a doubling of proteinuria (or albuminuria along with other end-organ features). This distinction is important, as the majority of these women are likely to develop end-organ disease manifestations (thrombocytopaenia [$<150\times10^3/mm^3$], elevated liver transaminases [plasma aspartate amino transaminase >40 U/l], elevated creatinine, headaches or visual symptoms, pulmonary oedema) or fetal problems with pre-term delivery [162].

Pre-eclampsia complicates 7–20% of pregnancies in women with type 1 diabetes, an approximately fivefold higher risk compared with women without diabetes. Pre-eclampsia is associated with hyperglycaemia in both early and late pregnancy [90, 91] and occurs most frequently in women with pre-existing hypertension and proteinuria due to diabetic nephropathy [91, 159]. Severe (early-onset) pre-eclampsia is associated with a significant risk of adverse maternal fetal outcomes, including impaired fetal growth, placental abruption, eclampsia, coagulation abnormalities, abnormal liver function, and even maternal death, with attendant needs of instrumental delivery and neonatal intensive care [158]. Early delivery is the most effective treatment, but adds to the morbidity from prematurity.

Blood pressure recommendations include a target of 140/90 mmHg and even below 135/85 mmHg before and during pregnancy in the hope of reducing the risks of pregnancy-induced hypertension, pre-eclampsia, and preterm birth [155, 164, 165]. Treatment of severe hypertension (≥160/110 mmHg) is needed to reduce the risk of maternal intracerebral haemorrhage and maternal death [165].

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are contraindicated in the second and third trimesters due to reports of severe impairment of renal development and function, oligohydramnios, limb contractures, lung hypoplasia, IUGR, and death [166, 167]. A meta-analysis, however, concluded that the risk of congenital malformations observed with ACE inhibitors (RR 1.78) was similar to that of other antihypertensive drugs (RR 1.45), and the risk of their use in the first trimester would therefore appear not to increase the risk of malformations additional to that of hypertension itself or other antihypertensive drugs. The common practice is to discontinue these drugs when pregnancy is confirmed rather than planned, as it may be equally hazardous to risk losing control of blood pressure and albuminuria.

Diabetic nephropathy

The prevalence of diabetic nephropathy in pregnant women with diabetes is 3–15% and 5–11% have microalbuminuria [155, 168]. Most studies relate to type 1 diabetes, but clinical findings are similar in women with type 2 diabetes [169]. Diabetic nephropathy affects the outcome of pregnancy by two main mechanisms:

• Development of severe maternal hypertension necessitating termination of pregnancy and thereby preterm delivery.

- Impaired placental development leading to fetal growth restriction and risk of stillbirth.

The pregnancy risk increases with the degree of renal impairment. The development of pre-eclampsia is the greatest hazard of diabetic nephropathy. Reported rates in women with type 1 diabetes are 6–10% with normal urinary albumin excretion, but increasing to 42% in women with microalbuminuria and 64% when diabetic nephropathy is present before or in early pregnancy [155, 157, 158].

The glomerular filtration rate (GFR) normally increases by 50–100% during pregnancy. In women with nephropathy, the GFR may increase only slightly during pregnancy, but there can be dramatic increases in protein excretion, especially in late pregnancy. After delivery, albumin excretion can remain high for a few weeks, but usually then falls to prepregnancy levels.

Pathophysiological factors in the development of pre-eclampsia in women with type 1 diabetes and diabetic nephropathy/microalbuminuria include endothelial dysfunction and impaired maximal vasodilatory capacity, activation of the RAS system, cardiac overload, and anti-angiogenic factors [169]. The majority of these factors can be modulated by antihypertensive treatment, in relation to both blood pressure and urinary albumin excretion.

It is important to screen for the development of pre-eclampsia in all pregnant women with diabetes. In women with underlying renal dysfunction, it may be reasonable to initiate antihypertensive treatment at lower thresholds and to focus on the level of albumin excretion [60] (target <140/90 and even 130/85 mmHg). In some centres this seems to be associated with improved pregnancy outcomes and fewer preterm deliveries [155], with similar results in type 2 diabetes [168, 169].

In general, pregnancy outcome is favourable, and there is no deterioration during pregnancy with modest elevations of serum creatinine (<124 µmol/l [1.4 mg/dl]), proteinuria <1 g/24 h, and normal blood pressure in early pregnancy, when tight antihypertensive management is achieved. By contrast, a serum creatinine above 176 µmol/l (2.0 mg/dl), severe hypertension or proteinuria in the nephrotic range (above 3 g/24 h), and/or pre-existing cardiovascular disease are associated with a high risk for poor maternal and fetal outcome [169].

Antihypertensive drugs

Methyldopa (a centrally acting α-adrenergic agonist), with over 40 years' experience, remains one of the most widely used drugs for the treatment of hypertension in pregnancy, with no apparent adverse effects on fetal well-being.

Other suitable agents include labetalol, a non-selective β-blocker with vascular α-receptor blocking capabilities, and calcium channel blockers, among which nifedipine has been the most extensively investigated. Nifedipine, labetalol, metoprolol, methyldopa, captopril, and enalapril are regarded as safe during breastfeeding [15, 60, 169].

In addition, NICE recommends that women with more than one moderate risk factor for pre-eclampsia should take 150 mg of aspirin daily from 12 weeks until the birth of the baby. As well as diabetes, moderate risk factors include first pregnancy, age 40 years or older, pregnancy interval of more than 10 years, BMI of ≥35 kg/m^2 at first visit, and a family history of pre-eclampsia or multiple pregnancy [15, 60]. This recommendation is not entirely consistent with evidence from the major clinical trials in which no benefit for aspirin was seen [60], and may explain why the recommendation is not promoted by all diabetes societies.

Supplementation with antioxidants (vitamins C and E) does not reduce the prevalence of pre-eclampsia in women with type 1 diabetes and is not generally recommended [90].

Renal transplantation

The first report of a successful pregnancy following renal transplantation for diabetic nephropathy was in 1986 [170]. Transplant registries suggest that successful pregnancies are now common [170, 171], but these data fail to distinguish pregnancy outcomes specific to diabetes. The reported incidence of diabetes during pregnancy in women with renal transplants ranges from 5% to 12% and the rate of hypertension prior to pregnancy from 40% to 72%, which may reflect pre-existing conditions leading to transplantation and/or to the side effects of required immunosuppressive drugs [172]. Pregnancy should be delayed for at least one year following transplantation to allow greater stability in graft function (serum creatinine <133 µmol/l, minimal proteinuria ≤500 mg/24 h) and maintenance immunosuppressive drugs, and women should be managed by a multidisciplinary team [15, 172]. Perinatal survival in these pregnancies is almost 75%, but a large percentage of pregnancies will be associated with increased maternal and perinatal complications, including miscarriage (15–20%), pre-eclampsia (30–35%), preterm delivery (50–55%), urinary tract infection (2–5%), fetal growth restriction (5–10%), rejection during pregnancy (35–40%) and graft rejection within two years after delivery (30–50%) [171, 172]. Management of these women is similar to diabetic nephropathy, with preconception care, frequent perinatal care, optimal glycaemic and blood pressure management, intensive fetal testing, and timely delivery being the keys to successful outcome [169, 172].

Neuropathy

Pregnancy does not affect the progression of peripheral or autonomic neuropathy, but severe gastroparesis due to autonomic neuropathy with variable nutrition, fluctuating insulin requirements, and frequent vomiting may present a major management challenge, resulting in pregnancy loss, maternal malnutrition, and higher rates of ketoacidosis in women with type 1 diabetes [173].

Ischaemic heart disease

Ischaemic heart disease in pregnancy is rare, but prevalence rates have increased in recent years. Ischaemic heart disease is now the commonest cause of cardiac death associated with pregnancy in the UK [15]. The risk is increased by a combination of maternal diabetes, obesity, and increasing age, with the highest rates occurring among those with longer duration of diabetes and type 2 diabetes.

Non-pregnant women with type 1 diabetes aged 35–45 years have a 15-fold higher risk of a major cardiovascular event, while women with type 2 diabetes aged 35–54 years have a fivefold increase of a myocardial infarction compared with women without diabetes of a similar age [174, 175]. Pregnancy increases the risk of an acute myocardial infarction 3–4-fold, with the greatest risk being peripartum [176].

Mortality rates from acute myocardial infarction in pregnancy in women with diabetes have declined, but the prognosis is poor, and such women require intensive management similar to that outside of pregnancy.

Bariatric surgery

Fertility increases following bariatric surgery [177], but women should preferably wait one year post-surgery before conception. The risk of hypertensive disorders of pregnancy [178] and GDM is

reduced following bariatric surgery and offspring are at lower risk of LGA but at higher risk of SGA. In a study from the Swedish Medical Birth Register involving 670 singleton pregnancies, a lower risk of GDM (1.9% vs 6.8%; OR 0.25; 95% CI 0.13 to 0.47; p <0.001) and LGA infants (8.6% vs 22.4%; OR 0.33; 95% CI 0.24 to 0.44; p <0.001) compared with BMI-matched women from the general population was reported [178]. Women should be monitored throughout pregnancy for micronutrient deficiency. Given that women may develop surgical complications during pregnancy, involvement of a bariatric surgeon is advisable.

Management of diabetes in pregnancy

There is broad consensus among the international bodies [15, 60, 179, 180] and the importance of pregnancy planning has been emphasized, as pre-pregnancy counselling improves outcomes. The key elements include optimizing glycaemia before conception, folate administration, smoking cessation, review of potentially teratogenic drugs, and management of diabetic complications. A multidisciplinary team, comprising an obstetrician, diabetologist, diabetes specialist midwife, diabetes specialist nurse, and diabetes specialist dietitian, within a secondary or tertiary care setting has been recommended for the care of pregnant women with type 1 diabetes, starting before pregnancy [15].

The overall aim of joint antenatal diabetes care is to allow the woman to have an enjoyable experience of pregnancy and delivery of a normal and healthy baby. This is best achieved by attendance for prepregnancy care, referral for specialist care immediately on diagnosis of pregnancy, two-weekly multidisciplinary reviews during pregnancy, and clear postnatal plans for contraception, with early referral back to her usual diabetes team [15]. Pregnancy care is designed to advise on the topics listed in Table 71.4.

Glycaemic targets before and during pregnancy

Elevated HbA_{1c} in the periconceptual period and first trimester increases the risk of pre-eclampsia, perinatal or neonatal death, and congenital malformations [9, 15, 60]. HbA_{1c} results during the second and third trimesters of pregnancy should be interpreted more cautiously, given altered red blood cell turnover, but high levels are associated with pre-eclampsia, preterm delivery, LGA, and NICU admission [91]. The level of risk increases with HbA_{1c} levels above 48 mmol/l [91].

International bodies recommend that women should test their capillary blood glucose fasting, pre-meals, one hour post-meals, and at bedtime during pregnancy, aiming if possible to achieve the glycaemic targets detailed in Table 71.5. These targets are demanding and many women do not reach them. The 2013 UK NDIPA [10] highlighted that only 13–15% of pregnant women with type 1 diabetes had target HbA_{1c} (<48 mmol/mol) in early pregnancy, rising to 35% in late pregnancy. In women with HbA_{1c} levels >48 mmol/mol after 24 weeks, preterm delivery, LGA, and NICU rates exceeded 50%, compared with 30% in women with levels <48 mmol/mol after 24 weeks [10].

The importance of achieving optimal glycaemic levels before and during pregnancy should be balanced against the risks of hypoglycaemia. Women with type 1 diabetes have an increased risk of hypoglycaemia in the first trimester and have an altered counter-regulatory response in pregnancy that may decrease hypoglycaemia awareness. Women with diabetes and family members need to be educated about the prevention, recognition, and treatment of hypoglycaemia before, during, and after pregnancy to help prevent and manage these risks.

In recognition of this, all guidelines advocate that targets should be relaxed if there is *undue* hypoglycaemia or impaired hypoglycaemia unawareness. Limited evidence suggests that moderate glucose levels (fasting glucose 5.0–6.5 mmol/l) are not inferior to lower levels [182]. In a large observational study, the risk of some adverse outcomes (macrosomia, pre-eclampsia, early delivery, and neonatal hypoglycaemia) was elevated only when the 26-week HbA_{1c} was ≥48 mmol (6.5%) [91].

Table 71.4 The components of pregnancy care.

Rapid referral to a joint antenatal diabetes clinic
Blood glucose targets and the rationale for excellent glycaemic management
Cessation of any potentially teratogenic medications
Folic acid usage: 5 mg/d (NICE and ES) or 0.6 mg/d (ADA)
Measurement of HbA_{1c} to assess risk of fetal abnormalities
Detection, monitoring, and management of diabetes-related complications
Accurate pregnancy dating and ultrasound detection of fetal abnormalities
Determination of the most appropriate time and mode of delivery
Management plan for blood glucose levels post-delivery

ADA, American Diabetes Association; ES, Endocrine Society; HbA_{1c}, glycated haemoglobin; NICE, National Institute for Health and Care Excellence.

Table 71.5 Glucose targets in the treatment of diabetes during pregnancy.

Organization	Target fasting glucose	Target 1 h post-prandial glucose	Target 2 h post-prandial glucose
NICE [15]	<5.3 mmol/l	<7.8 mmol/l	<6.4 mmol/l
ADA [50]	<5.3 mmol/l	<7.8 mmol/l	<6.7 mmol/l
Diabetes Canada [180]	<5.3 mmol/l	<7.8 mmol/l	<6.7 mmol/l
ADIPS [181]	≤5.0 mmol/l	≤7.4 mmol/l	≤6.7 mmol/l

ADA, American Diabetes Association; ADIPS, Australasian Diabetes in Pregnancy Society; NICE, National Institute for Health and Care Excellence.

Relation of glycated haemoglobin and pre- and post-prandial glucose levels to maternal fetal outcome

While the benefits of near-normal glycaemia both before and during pregnancy are universally recognized [142], the optimal means to achieve this is unknown. The relevance of post-prandial glucose excursions to adverse maternal outcomes is supported by two randomized trials, which reported that effectively managing post-prandial glucose levels was more likely to be associated with a successful pregnancy outcome than controlling fasting glucose levels [183, 184]. In addition, spikes of high glucose values (>11 mmol/l) are a strong predictor for LGA/macrosomia [185].

Continuous glucose monitoring systems in pregnancy

CGM systems highlight the fluctuation of glucose levels, including nocturnally, which may not be appreciated by conventional pre- and post-prandial capillary blood glucose monitoring [186, 187].

Improved sensors, together with an evolving consensus on the interpretation of CGM, have resulted in this technology gaining acceptance as a valid clinical measure of blood glucose, and being accepted as an endpoint in clinical trials [188].

Pregnant women with type 1 diabetes using standard pumps and pens spend only 12 h/d with near-normal glucose levels (50% time in target during pregnancy). They spend 10 h/d above the NICE recommended glucose target 3.9–7.8 mmol/l (40% of the time too high), and 2 h/d below target (10% of the time too low) [189]. By the third trimester maternal hyperglycaemia improves only slightly, even with frequent antenatal clinic visits.

A randomized controlled trial (RCT) evaluating CGM with or without conventional glucose monitoring every 4–6 weeks between 8 and 32 weeks' gestation, in 46 women with type 1 diabetes and 25 with type 2 diabetes, showed an improvement in mean HbA_{1c} in late pregnancy (5.8% vs 6.4% [40 mmol/mol vs 48 mmol/mol]; p = 0.0007), with lower LGA rates (35% vs 60%) compared with conventional monitoring [190]. By contrast, a subsequent Danish RCT of intermittent real-time CGM (RT-CGM) versus self-monitored plasma glucose seven times daily showed no improvement in glycaemic levels or pregnancy outcomes in women with pregestational diabetes. However, both groups of women had low HbA_{1c} at conception (6.6 vs 6.8% [49 vs 51 mmol/mol]), and in 60% use of RT-CGM was intermittent [191].

A recent multicentre trial (Continuous glucose monitoring in pregnant women with type 1 diabetes, CONCEPTT) showed that those randomized to RT-CGM compared with standard care had a reduction in HbA_{1c} (0.19% [2 mmol/mol], p = 0.021), more time in range (TIR) (68% vs 61%; p = 0.003), and less time hyperglycaemic (27% vs 32%; p = 0.028), although with no difference in severe hypoglycaemic episodes [192]. In addition, there was a lower incidence of LGA (OR 0.51; p = 0.021), fewer NICU admissions lasting more than 24 hours (OR 0.48; 95% CI 0.26 to 0.86; p = 0.016), fewer incidents of neonatal hypoglycaemia (OR 0.45; 95% CI 0.22 to 0.89; p = 0.025), and one day shorter length of hospital stay (p = 0.009). There was no apparent benefit of CGM in women planning pregnancy.

An observational cohort study that evaluated the glycaemic variables reported using CGM found that lower mean glucose, lower standard deviation, and higher percentage of TIR were associated with a lower risk for LGA births and other adverse neonatal outcomes [193].

These studies support a role for CGM in the management of pregnant women with type 1 diabetes, possibly in preference to pump therapy, given the lack of difference between pump and multiple daily injection groups. Trials are in progress to evaluate closed-loop insulin delivery systems compared with conventional methods; however, preliminary data suggest that TIR during the day is no greater with these devices than with CGM, and greater emphasis may be needed on very fast-acting insulin analogues to reduce post-prandial glucose excursions. Adverse reactions (particularly skin) from CGM devices are high and may limit usage or even the reliability of readings [194].

The international consensus on TIR [195] endorses pregnancy target ranges and goals for TIR for women with type 1 diabetes including those using CGM, as reported on the ambulatory glucose profile:

- Time in range (3.5–7.8 mmol/l [63–140 mg/dl]; goal >70%).
- Time below range (<3.5 mmol/l) [<63 mg/dl]; goal 4%).
- Time below range (<3 mmol/l [54 mg/dl]; goal <1%).
- Time above range (>7.8 mmol/l [>140 mg/dl]; goal <25%).

Use of CGM-reported mean glucose is superior to the use of estimated HbA_{1c}, glucose management indicator, and other calculations to estimate HbA_{1c} given the changes to HbA_{1c} that occur during pregnancy [196]. TIR can be used to assess glycaemia in women with type 1 diabetes, but it does not provide actionable data to address fasting and post-prandial hypoglycaemia or hyperglycaemia. Universally, the cost of this technology is likely to restrict its use to selected, educated, motivated women in experienced centres receiving dedicated supervision. There are no data to support the use of TIR in women with type 2 diabetes or GDM. NICE has recently advised that CGM should be offered to all pregnant women on insulin therapy, and particularly to those with problematic severe hypoglycaemia (with or without impaired hypoglycaemic awareness) or who have unstable blood glucose levels (to reduce variability), or to gain information about glucose variability [15]. The American Diabetes Association (ADA) recommends CGM for selected women such as those with hypoglycaemic unawareness [60].

Monitoring of diabetes-related complications

Monitoring of diabetes-related complications is important to identify those women at risk of retinopathy progression and because of the association of nephropathy with pre-eclampsia and fetal growth retardation.

Retinal assessment

All guidelines recommend that any necessary treatment for retinopathy is completed and the clinical condition is stable before embarking on pregnancy. NICE guidance recommends retinal photographic screening at booking and at 28 weeks' gestation in all women with pre-existing diabetes, with more intensive follow-up at 16–20 weeks in those with any retinopathy at booking [15]. The ADA similarly recommends that women with no or minimal retinopathy on initial screening should have follow-up retinal examination in the third trimester, that those with mild retinopathy be evaluated every trimester, and that those with more advanced retinal disease should be evaluated at intervals determined by the ophthalmologist [60]. The Endocrine Society recommends ocular assessment soon after conception and then 'periodically as indicated', implying more intensive follow-up in women with established retinopathy [179].

Proliferative retinopathy should be treated with scatter or pan retinal photocoagulation as per routine guidelines. Occasional reports of intraocular anti-VEGF during pregnancy have been reported with no adverse events, but the safety of these agents during pregnancy is unknown and there are theoretical concerns regarding the deleterious effects of anti-VEGF drugs on fetal vasculogenesis and worsening of pre-eclampsia. Women with GDM are not at increased risk for diabetic retinopathy during pregnancy and do not require additional ophthalmic evaluation.

Hypertension/nephropathy

In women with pre-existing diabetes, NICE recommends that renal assessment should occur at booking if not undertaken in the previous 12 months [15]. If the serum creatinine is abnormal (≥120 μmol/l), the urine-to-albumin creatinine ratio is >30 g/mol, or the total protein excretion exceeds 2 g/d, referral to a nephrologist should be considered. Women with known renal disease should be carefully monitored with regular blood pressure, urine albumin/protein excretion measurements, and serum creatinine. A rising serum creatinine has serious implications. Suitable antihypertensive

agents should be started with target blood pressure <130/85 mmHg [60]. NICE suggests that thromboprophylaxis should be considered for women with proteinuria >5 g/d [15, 169].

Drug cessation

Teratogenic drugs, such as ACE inhibitors and ARBs, should be discontinued before contraception, or as soon as pregnancy is confirmed, and alternative antihypertensive agents suitable for use during pregnancy should be substituted [15]. Statins should be discontinued before pregnancy or as soon as pregnancy is confirmed [15, 60]. Smoking cessation should be encouraged.

Obesity

NICE recommends that women with diabetes with a BMI >27 kg/m^2 who are planning to become pregnant should be advised to lose weight.

Autoimmune disease

Up to one-third of women with type 1 diabetes have serological evidence of hypothyroidism, and up to half of these develop postpartum thyroiditis [197]. The Endocrine Society and ADA recommend pre- or early pregnancy screening of women with type 1 diabetes with thyroid-stimulating hormone (TSH) and thyroid antibody tests, with consideration also of testing for vitamin B_{12} deficiency. NICE makes no specific recommendation [15].

Insulin management

The physiology of pregnancy necessitates frequent titration of insulin to match changing requirements and emphasizes the importance of daily and frequent self-monitoring of blood glucose [198, 199]. During the first trimester, a time of enhanced insulin sensitivity and lower glucose levels, women may have lower insulin requirements (frequently compounded by pregnancy-associated sickness and altered hypoglycaemic awareness). From around 16 weeks, insulin resistance increases and total daily insulin doses increase linearly at approximately 5% per week until 36 weeks' gestation. This usually results in a doubling of the daily insulin dose compared with pre-pregnancy requirements and is closely related to weight gain [192, 198]. In women using continuous insulin infusion pumps, both basal and bolus doses increase, but the proportionate increase is greater for bolus doses [199, 200]. Insulin requirements usually level off towards the end of pregnancy; however, a rapid reduction in requirements can indicate the development of placental insufficiency and may merit early delivery [201]. Following delivery, insulin requirements rapidly fall, with doses in women with type 1 diabetes averaging two-thirds of the prepregnancy insulin dose or one-third of the dose at the end of pregnancy by the third postpartum day, and being similar to prepregnancy by the end of the first postpartum week [201]. In the majority of women with type 2 diabetes and GDM where insulin was started during pregnancy, it can be stopped after delivery.

Insulin regimens

None of the currently available insulin human preparations has been demonstrated to cross the placenta [60]. A recent Cochrane systematic review was unable to recommend any specific insulin regimen over another for the treatment of diabetes in pregnancy [202].

Most women with insulin-treated diabetes before pregnancy are using a multiple-dose insulin (MDI) regimen comprising a short-acting prandial insulin and an intermediate or long-acting insulin up to three times daily. Safety and efficacy data of analogue insulins have largely come from observational studies, but a large RCT of insulin aspart versus regular soluble insulin in type 1 diabetes showed similar efficacy, with a tendency to lower rates of hypoglycaemia and without apparent toxicity [203].

All guidelines now recommend a quick-acting insulin analogue, such as aspart or lispro, for mealtime coverage. There is less consensus about the choice of basal insulin. NICE recommends isophane insulin as the first choice, while the ADA prefers insulins studied in RCTs [15], but the Endocrine Society recommends that women already using insulin detemir or glargine continue these agents throughout pregnancy [179]. An RCT of 310 women with type 1 diabetes randomized to insulin detemir or neutral protamine Hagedorn (NPH) insulin (both with mealtime insulin aspart) revealed non-inferior HbA_{1c} values [204] and lower fasting glucose at 24 and 36 weeks with detemir (US Food and Drug Administration and European Medicines Agency approved) than with NPH, but pregnancy outcomes did not differ. The safety of insulin glargine data come from post-marketing surveillance. The recommendation is that women with diabetes successfully treated with the long-acting analogues preconception continue with this therapy.

The pharmacokinetic properties of faster insulin aspart (onset of appearance in bloodstream 4 min) and insulin degludec (half-life 25 h) analogues have a particular conceptual appeal in pregnancy, with their potential to reduce post-prandial glycaemic excursions and hypoglycaemia. In non-pregnant adults with type 1 diabetes, prandial faster insulin aspart was associated with improved one-hour post-prandial glucose levels versus standard aspart and significantly reduced HbA_{1c}, while a 12-month RCT of degludec/aspart versus glargine/aspart was associated with significant reductions in nocturnal hypoglycaemia and HbA_{1c} compared with glargine. Faster insulin aspart is deemed safe in pregnancy. A further study comparing insulin degludec to insulin detemir, together with insulin aspart, in pregnant women with type 1 diabetes is ongoing.

Continuous subcutaneous insulin infusion

CSII may be of use for selected women, such as those with a pronounced *dawn phenomenon* or recurrent hypoglycaemia, but there is little evidence supporting its routine use in pregnancy [205–207]. A meta-analysis of six studies (107 CSII vs 106 MDI) showed comparable glucose levels and pregnancy outcomes [208], although these studies were in the pre-analogue era, lacked power to detect differences in neonatal outcomes, and were likely to be confounded by selection bias. The UK NDIPA showed no difference in glycaemic levels or maternal fetal health outcomes between standard pump users (30% of women with type 1 diabetes) and pens (70%). Both groups had elevated mean HbA_{1c} (pump 51 mmol/mol vs pen 52 mmol/mol) after 24 weeks [57]. There are also some risks, which include hyperglycaemia or ketoacidosis in the event of pump failure and increased costs. Women whose diabetes is well managed with CSII before conception usually choose to continue it during pregnancy.

The expectation that closed-loop technology calibrated for pregnancy fasting and post-prandial glycaemic targets might offer

additional benefits to existing delivery systems during pregnancy was examined in a recent open-label, crossover study. Women with overnight closed loop were in target range (3.5–7.8 mmol/l) for 75% of the time overnight compared with 60% with sensor-augmented pump therapy [209]. There was also a reduction in hypoglycaemia and high TIR (closed loop 66%, sensor-augmented pump therapy 57%) when both day and night periods were included. These devices may reduce hypoglycaemia and allow more aggressive prandial target dosing [60].

Sick-day rules

All women should be advised on contingencies when they are not eating and drinking because of illness. Advice includes the following key reminders:

- Continue fluid intake if possible.
- Never stop taking their insulin.
- Frequent need for supplementary insulin doses as guided by intensive home blood glucose monitoring.

Emergency 24-hour access to diabetes team members is essential and there should be a low threshold for hospital admission. Both NICE and ADA recommend that women with type 1 diabetes should be issued with ketone strips to use if they become ill and/or hyperglycaemic [15, 60]. Women who are unable to eat often require 10% dextrose with an insulin drip to meet adequately the higher carbohydrate demands of the placenta and fetus in the third trimester to resolve their ketosis.

Type 2 diabetes versus type 1 diabetes

Type 2 diabetes in pregnancy was uncommon until the 1980s, but is being encountered with increasing frequency [210]. The IDF figures suggest that prevalence estimates range from 2% in 20–24-year-olds up to 7% in 40–44-year-olds [5]. The prevalence of type 2 diabetes in 10–19-year-olds rose by 30% over a 10-year period [210] and this was accompanied by increasing rates of obesity, including at younger ages, and of women choosing to delay pregnancy when their risk of type 2 diabetes was increased at the time of pregnancy. This has resulted in a change in the proportion of women with type 1 diabetes and type 2 diabetes during pregnancy. For example, in the UK in 2002–2003, type 2 diabetes accounted for 27% of pregestational diabetes [9]; in 2014 this increased to 47% [10]; and it was 50% in the most recent report in 2021 [57].

Compared with women with type 1 diabetes, pregnant women with type 2 diabetes tend to be older, have higher rates of obesity and comorbidities, greater ethnic diversity, and greater socioeconomic deprivation. In addition, they frequently present late to diabetes services and have lower rates of referral and attendance for prepregnancy counselling. While women with type 2 diabetes have lower glucose concentrations, fewer preterm births, fewer LGA babies, and fewer caesarean sections [7, 57], adverse pregnancy outcomes (congenital anomaly, still birth, neonatal death) [49, 50, 54] are at least similar to women with type 1 diabetes [7, 49, 57], with some reports suggesting higher perinatal mortality (OR 1.50; CI 1.15 to 1.96) [57].

A report of the first five years of the NDIPA across 172 maternity clinics in England, Wales, and the Isle of Man [57], involving 17 375 pregnancy outcomes in 15 290 pregnant women (50% type 1 diabetes; 50% type 2 diabetes), showed that women with type 2 diabetes had:

- Higher rates of preterm delivery (42% vs 23%; $p < 0.001$).
- Higher rates of LGA (52% vs 26% respectively; $p < 0.001$).
- Similar rates of congenital anomaly (44.8/1000 vs 40.5/1000; $p = 0.17$)
- Similar rates of still birth (10.4/1000 vs 13.5/1000; $p = 0.072$).
- Higher rates of neonatal death (7.4/1000 type 2 vs 11.2/1000 type 1; $p = 0.013$).

Independent risk factors for perinatal death were third-trimester HbA_{1c}, deprivation quintile, and having type 2 diabetes; maternal glycaemia and BMI were key modifiable risk factors.

The different contributions of risk factors to obstetric complications and adverse pregnancy outcomes in women with type 1 diabetes or type 2 diabetes are unclear. For the latter, the NDIPA highlighted lower rates of folic acid use and lower rates of prepregnancy counselling indicating problems with pregnancy planning, with most of women with type 2 diabetes having community-based diabetes care. At diagnosis, 6–7% of women with type 2 diabetes have microalbuminuria, up to 20% have retinopathy, up to 70% dyslipidaemia, 80+% have obesity, and around one-third have hypertension, in large part due to the metabolic syndrome [211]. Vascular complications are more common in type 2 diabetes and are related to adverse outcomes.

The management of type 2 diabetes in pregnancy is similar to that of type 1 diabetes. Many women are taking oral anti-diabetes drugs (e.g. metformin, sulfonylureas, or other agents) and cardiovascular drugs at the time of conception. The majority (>95%) of women with type 2 diabetes need insulin, often in high doses because of obesity. With the exception of metformin, all other oral anti-diabetes agents should be stopped, as their safety has not been determined. A large Canadian RCT examined the addition of metformin or placebo to standard insulin therapy in 502 women with type 2 diabetes. The results showed reduced maternal weight gain and insulin dosage, improved glycaemic levels, lower adiposity and infant size measurements (resulting in fewer large infants), but a higher proportion of SGA infants and no difference in a composite neonatal outcome between the two groups [212]. Currently NICE guidance approves metformin for use during pregnancy and breastfeeding [15]. The ADA guidelines, by contrast, suggest that insulin is the preferred medication to achieve glycaemia during pregnancy [60].

Type 2 diabetes is often associated with obesity. Recommended weight gain during pregnancy for women with overweight is 7–11 kg and for women with obesity is 4.5–9 kg [213] (Table 71.6). There are no adequate data on optimal weight gain versus weight maintenance in women with BMI >35 kg/m^2.

Obstetric surveillance

The goal of obstetric surveillance is to identify the fetus at risk, in order to intervene in a timely and appropriate fashion to reduce perinatal morbidity and mortality. Accurate dating of the pregnancy is an imperative and is best achieved by ultrasound examination at 8–10 weeks. Fetal monitoring in women with diabetes is as per routine antenatal care and includes a 20-week anomaly scan and fetal cardiac scan. The UK guideline [15] recommends ultrasound monitoring of fetal growth and amniotic fluid volume every

Table 71.6 Institute of Medicine recommendations for weight gain during pregnancy [213].

Weight category (prepregnancy or <10 weeks' gestation)	Body Mass Index (BMI; kg/m^2)	Recommended range of total weight gain (kg)	Recommended rate of weight gain in 2nd and 3rd trimesters (mean/ range; kg/week)
Underweight	<18.5	13–18	0.45 (0.45–0.59)
Normal weight	18.5–24.9	11–16	0.45 (0.36–0.45)
Overweight	25.0–29.9	7–15	0.25 (0.23–0.27)
Obese (grade 1)	30.0–34.9	5–9	0.23 (0.18–0.27)
Obese (other)	≥35.0	<5	<0.20

Calculations assume a 0.5–2.0 kg weight gain in the first trimester.
Source: Based on Institute of Medicine and National Research Council 2009 [213].

four weeks from 28 to 36 weeks and individualized monitoring of fetal well-being for women at risk of IUGR, and those with macrovascular disease or nephropathy. Tests of fetal well-being before 38 weeks (such as performing a biophysical profile and Doppler studies) are not recommended unless there is a risk of IUGR.

Additional appointments for obstetric visits requiring ultrasound examination should be determined on an individual basis, but virtual (remote) contact by telephone/email in uncomplicated pregnancies is likely to reduce unnecessary clinic visits. More frequent face-to-face reviews are needed towards the end of pregnancy to monitor for pre-eclampsia and to discuss the timing and mode of delivery. Women with problematic glycaemia, diabetes-related complications, and fetal growth abnormalities need more intense surveillance.

Labour and delivery

The primary objectives are to avoid fetal death *in utero* and the hazards of obstructed labour or shoulder dystocia associated with fetal macrosomia. Caesarean section rates for women with pregestational diabetes in most parts of the world are over 50% (65% in the 2013 NDIPA [10]) and are similar in type 1 diabetes and type 2 diabetes [57]. The rates of preterm birth (delivery at <37 weeks' gestation) are 2–3-fold higher among women with pregestational diabetes than among women without diabetes. The majority of this increase is due to elective preterm delivery (6–7-fold higher than in women without diabetes), but spontaneous preterm delivery is also increased (~50% higher). Iatrogenic prematurity has resulted in high rates of admission to the NICU in type 1 diabetes.

Given the increased risk of preterm delivery, LGA, and perinatal mortality, close surveillance of both mother and baby by an experienced obstetrician is needed during delivery. The timing and mode of birth should be discussed with the woman during her antenatal appointments. An individualized approach is required, with particular consideration to fetal well-being, estimated size, glycaemic management, diabetes complications, and past obstetric history. NICE guidelines advise that women with type 1 diabetes should be offered an elective delivery between 37 + 0 and 38 + 6 weeks gestation, assuming that no other significant factors have developed before this time. An elective birth before 37 + 0 weeks should be considered if significant metabolic or any other maternal or fetal complications occur [15].

Nulliparity, progression of nephropathy, pre-eclampsia, and HbA_{1c} ≥53 mmol/mol (7%) at delivery are all strongly associated with preterm delivery, as is poorer maternal mental health [214]. Preterm delivery is associated with significant neonatal morbidity, particularly neonatal hypoglycaemia and respiratory distress syndrome [215].

Preterm labour can be particularly hazardous for infants of women with diabetes. β-sympathomimetic agents used to suppress uterine contractions, and corticosteroids used to accelerate fetal lung maturation, may result in significant and prolonged maternal hyperglycaemia, and even ketoacidosis, and the need for supplementary insulin must be anticipated. Several algorithms to guide glycaemic management during steroid therapy have been developed [216, 217]. Admission to hospital and close supervision are essential.

The management of labour should follow standard practice. Given the desire not to prolong pregnancy unduly, induction of labour is widely utilized and usually involves a combination of prostaglandins initially followed frequently by oxytocin. Careful monitoring of progress is facilitated by a partograph and continuous electronic fetal monitoring by cardiotocography.

Management of diabetes during labour should follow an established protocol adapted for time and mode of delivery in a dedicated centre with a NICU equipped and staffed to deliver the most sophisticated level of care (Table 71.7). Women with type 1 diabetes who use CSII should have the opportunity to discuss glycaemic management during labour in advance of delivery with their physician, and an individualized plan should be clearly documented in their chart. NICE guidelines recommend maintenance of maternal blood glucose between 4 and 7 mmol/l during labour and delivery

Table 71.7 Intradelivery protocol and method of delivery.

Elective caesarean section
Women with type 1 diabetes should be placed first on the operating list and admitted either the previous day or early on the morning of surgery
Women should fast from 22:00 the evening before surgery
Long-acting insulin is taken as normal prior to a light supper
Rapid-acting insulin should be withheld on the day of surgery
1–2 h prior to surgery, hourly monitoring of blood glucose begins; and a glucose insulin infusion is commenced, if necessary, to maintain blood glucose between 4 and 7 mmol/l
Insulin dose and/or rate are adjusted in response to maternal/capillary glucose
Induction of labour
Women should continue their current insulin regimen until labour is confirmed
Often an early-morning breakfast is consumed with their normal morning insulin dose
Once labour is confirmed and the woman is fasting, glucose-insulin infusion is commenced as per protocol, unless delivery is imminent
Maternal blood glucose levels should be monitored hourly
Blood glucose levels should be maintained between 4 and 7 mmol/l
Insulin dose and/or rate are adjusted in response to maternal blood glucose
Spontaneous labour
Following admission in spontaneous labour, the woman is fasted
Blood glucose level should be taken on admission and hourly thereafter
Once labour is confirmed, a glucose-insulin infusion is commenced as per protocol
Capillary glucose levels should be maintained between 4 and 7 mmol/l
Insulin dose and/or rate are adjusted according to the local protocol in response to maternal blood glucose

to reduce the incidence of both neonatal hypoglycaemia and fetal distress [15, 217]. Hourly capillary glucose measurements provide a ready guide to the success of management and the need for insulin adjustment. Commonly used regimens (in the absence of a consensus) involve a constant glucose infusion with insulin being infused separately by an infusion pump. Women who are using CSII may continue their basal infusion during labour, but it is essential that whatever regimen is used, midwifery and anaesthetic staff are familiar with it.

Management of diabetes postpartum

Insulin sensitivity increases in the immediate postpartum period, normalizing over the following 1–2 weeks. Once the cord is cut, any insulin infusion should be reduced by 50%, with regular capillary blood glucose measurement and administration of intravenous fluids until the mother is eating normally. This should be done with close supervision by the diabetes care team and insulin titration as required. The women should be encouraged to eat a small snack before breastfeeding to avoid hypoglycaemia. Insulin requirements may increase during the day due to increased caloric intake, with a fall in nocturnal insulin requirements due to glucose siphoning into the breast milk. Women are therefore advised to reduce their long-acting insulin when breastfeeding. Maternal glucose should be kept as normal as possible to avoid elevations in milk glucose and maternal hypoglycaemia. This is achieved through regular snacking and careful insulin adjustment with full support from the diabetes specialist team.

Breastfeeding

Breastfeeding rates are often disappointingly low despite encouragement [218, 219]. Relevant factors include admission to neonatal care with separation of mothers from their babies, which makes it difficult to establish breastfeeding. Higher educational attainment and previous positive experiences of breastfeeding are strong predictors of success [219, 220]. In women who need insulin, the postpartum insulin requirements during breastfeeding are typically approximately 10% lower than before pregnancy. For women with type 2 diabetes, metformin is approved during breastfeeding, as the levels appearing in breast milk are low [15].

Neonatal care

Neonates born to women with type 1 diabetes should have their blood glucose measured using a method validated for neonatal use. Women should feed their babies within 30 minutes of birth and then at frequent intervals (every 2–3 hours) until feeding maintains pre-feeding capillary plasma glucose levels at a minimum of 2.0 mmol/l. If capillary plasma glucose values are below 2.0 mmol/l on two consecutive readings, despite maximal support for feeding, if there are abnormal clinical signs, or if the baby will not feed orally effectively, additional measures, such as tube feeding or intravenous dextrose, should be used. Up to 50% of babies may need admission for neonatal intensive care [41] for the indications in Table 71.8. Neonates should not be transferred to community care until they are at least 24 hours old, are maintaining their blood glucose at a normal level, and are feeding well.

Table 71.8 Neonatal complications after diabetes in pregnancy.

Directly related to diabetes in pregnancy
Congenital anomalies
Intrauterine growth restriction
Intrapartum hypoxia–ischaemia
Macrosomia, obstructed labour, birth injury
Neonatal death
Polycythaemia/jaundice
Hypoketonaemia, hypoglycaemia
Hypocalcaemia, hypomagnesaemia
Hypertrophic cardiomyopathy
Complications of necessary, or unnecessary, obstetric interventions
Complications of preterm delivery
Complications of caesarean section – respiratory distress, impact on breastfeeding
Iatrogenic
Inappropriate separation of mother and baby
Inappropriate formula supplementation – impact on breastfeeding

Contraception

The discussion about family planning should begin before delivery, particularly if caesarean section is likely, as many women elect to have tubal ligation at the time of their caesarean section; it should also be an essential component of early postpregnancy counselling.

There is a growing opinion that contraception should be initiated before the woman is discharged from hospital. This is due to the recognition that ovulation and sexual activity occur much earlier than previously estimated. In addition, many women miss their postpartum appointments. The WHO has stated that virtually all methods of contraception can be offered to women with type 1 diabetes [221]. However, oestrogen-containing methods should be avoided by women with diabetes-related complications such as retinopathy, nephropathy, or cardiovascular disease. Intrauterine contraceptive methods (IUDs) are particularly suited to women who do not wish to become pregnant within the next year. In women without vascular disease who wish to conceive sooner, combined (oestrogen and progesterone) hormonal contraception is safe. The lowest dose (oestrogen <35 mg) and potency formulation should be used, as the absolute increase in arterial thromboembolism is very low (1/12 000) and comparable to that among users without diabetes and non-users. Barrier and natural family planning methods are less ideal because of high failure rates. Long-acting reversable contraception may be ideal for many women. The risk of unplanned pregnancy outweighs the risk of any given contraception option. Following completion of childbearing, vasectomy and female sterilization are available.

Women with type 1 diabetes should revert to their routine diabetes care under the supervision of their diabetes care team. Women planning further pregnancies should be reminded of the need for preconception planning for optimal pregnancy outcome.

Gestational diabetes mellitus

In contrast to the clearly established association between overt diabetes during pregnancy and adverse pregnancy outcomes, few areas have aroused such controversy as the concept of GDM [222, 223].

For decades its validity has been questioned and confusion generated over disparate approaches to diagnosis and screening [223]. Following the publication of landmark observational clinical trials and RCTs and consensus IADPSG/WHO criteria in 2013 [41, 42], significant progress towards a universal approach to diagnosis was made, but the subject remains one of active debate. The prevalence of GDM is increasing, and globally is now estimated to affect more than 20 million live births (about 1 in 6), mainly in low- and middle-income countries, where most of the morbidity and mortality occur [5]. Obesity is fuelling a rise in GDM and is itself a risk factor for adverse pregnancy outcomes. Increasing recognition that accelerated fetal growth and fat accretion and maternal biochemical abnormalities are already detectable by 20 weeks has generated ongoing research into the virtue of earlier diagnosis than the traditional 28 weeks' gestation, which in turn might allow a greater window for meaningful therapeutic intervention. GDM is associated with significant long-term metabolic and cardiovascular risks for both mother and offspring, with urgent implications for public health prevention.

The first documented case was possibly that of a pregnant women in 1823 with new onset of thirst and glycosuria, which resulted in the delivery of a dead macrosomic baby [224]. The exact origin of the term *gestational diabetes* is difficult to ascertain, but almost certainly grew from a realization of the relationship between fetal survival, birth weight, and hyperglycaemia during pregnancy [225, 226]. The term was used by Pedersen and others towards the end of the 1960s [33].

The first major prospective studies of carbohydrate metabolism in pregnancy were carried out in North America in the 1950s [227, 228]. In a notable study by O'Sullivan and Mahan in 1964 [229], glucose was measured fasting, and at one hour, two hours, and three hours after a 100 g OGTT in an unselected group of 752 pregnant women (45% in second trimester and 52% in third trimester) recruited on registration in a Boston hospital. Those with values two standard deviations above the mean at each threshold (with two threshold values needing to be equalled or exceeded for diagnosis) had the best predictive value for the subsequent diagnosis of diabetes (using US Public Health Service Criteria). In a second older cohort of 1013 non-pregnant women, 2% of these women developed GDM over an eight-year period (again using US Public Health Service Criteria). Additional studies showed that women meeting this definition of GDM had a fourfold increase in perinatal mortality [230] and an increase in maternal diabetes up to 16 years later [231].

These threshold values were later modified by Carpenter and Coustan [232] to allow for varying assay techniques (use of enzyme vs reducing substances and plasma vs whole blood), subsequently endorsed by the US National Diabetes Data Group [233], and used to diagnose GDM in the USA for the next four to five decades and even to the present day (Table 71.9).

The original concept of GDM required it to be a temporary state with return to normal after delivery and that was the definition used by Pedersen in his pioneering book *The Pregnancy Diabetic and Her Newborn* [33]. More formal efforts to standardize terminology and diagnostic thresholds did not take place until the end of the 1970s, coincidental with an increasing focus on the diagnostic criteria for diabetes outside pregnancy both within the USA [235] and internationally [236, 237].

Currently, the ADA defines GDM as 'carbohydrate intolerance of varying severity with onset or first recognition during pregnancy' [60]. This definition, which emanated from international workshops spanning several decades, applies irrespective of whether or not insulin is used for treatment, or the condition persists after pregnancy. Universal screening employing a 100 g OGTT after 24 weeks' gestation (preceded by a 50 g glucose challenge test) is recommended, using the Carpenter and Coustan modification of the O'Sullivan and Mahan criteria [60, 235] (Table 71.9). During the 1980s and 1990s there was increasing recognition that GDM was likely to include women who had unrecognized diabetes before the index pregnancy.

The WHO originally defined diabetes mellitus as 'a state of chronic hyperglycaemia' on the basis of guidelines used for non-pregnant adults [236], and included an additional category of gestational impaired glucose tolerance (fasting plasma glucose [FPG] ≥7.8 mmol/l and two hours post OGTT ≥7.8 mmol/l). This

Table 71.9 Criteria for diagnosis of gestational diabetes with oral glucose tolerance test (OGTT).

Organization	Recommended approach	Fasting threshold (mmol/l)	1 h threshold (mmol/l)	2 h threshold (mmol/l)	3 h threshold (mmol/l)
IADPSG [41]; ADIPS [181]; WHO [214]; FIGO [40]	One-step 2 h, 75 g OGTT	≥5.1	≥10.0	≥8.5	NA
ADA [60]	Two-step 100 g, 3 h, OGTT[a]	≥5.3	≥10.0	≥8.6	≥7.8
	or				
	One-step 2 h, 75 g OGTT	≥5.1	≥10.0	≥8.5	NA
ACOG/C-C [234]	Two-step 3 h, 100 g OGTT[a]	≥5.3	≥10.0	≥8.6	≥7.8
NICE [15]	One-step 2 h, 75 g OGTT	≥5.6	NA	≥7.8	NA
Diabetes Canada [180]	Two-step 2 h, 75 g OGTT (preferred)	≥5.3	≥10.6	≥9.0	NA
	or				
	One-step 2 h, 75 g OGTT	≥5.1	≥10.0	≥8.5	NA
NDDG [13]	Two-step 3 h, 100 g OGTT[a]	≥5.8	≥10.6	≥9.2	≥8.0
O'Sullivan [229]	Two-step 3 h, 100 g OGTT[a]	≥5.0	≥9.2	≥8.1	≥6.9

[a] Two must be equalled or exceeded for diagnosis of gestational diabetes.
ACOG, American College of Obstetricians and Gynaecologists; ADA, American Diabetes Association; C and C, Carpenter and Coustan criteria; IADPSG, International Association for Diabetes in Pregnancy Study Groups; NA, no applicable value; NDDG, National Diabetes Data Group; NICE, National Institute for Health and Care Excellence; WHO, World Health Organization.

latter definition was applicable only to women in whom these criteria are first detected during pregnancy. In 1998, the definition was refined to that currently in use [237] when it was recommended that only women with risk factors should undergo OGTT testing. However, national guideline groups from different countries frequently adopted their own modifications of the US and WHO approaches (Table 71.9), resulting in much confusion and perpetuating a lack of international consensus and meaningful epidemiological comparison.

It was against this background that the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study [238] was designed specifically to examine the relevance of minor degrees of hyperglycaemia during pregnancy, short of diabetes, to adverse maternal and fetal outcome. This multicentre, multicultural observational study involved 23 000 pregnant women undergoing a 75 g OGTT at 24–32 weeks' gestation. Clinicians were blinded to the results unless prespecified thresholds were exceeded (fasting glucose >5.8 mmol/l; two-hour glucose >11.1 mmol/l or a random glucose later in gestation >8.9 mmol/l), and these women were excluded. The study showed continuous independent relationships [238–240] between untreated maternal glucose levels (fasting, one hour, and two hours post glucose load) and each of the primary outcomes: birth weight >90th centile, clinical neonatal hypoglycaemia, primary caesarean section, and cord C-peptide levels (reflecting fetal hyperinsulinaemia) (Figure 71.2). Birth weight and cord C-peptide had the strongest association with maternal glucose. Mean birth weight differences between the highest and lowest glucose categories for the three time points ranged from 242 g to 305 g. Among the secondary outcomes, shoulder dystocia and pre-eclampsia were positively associated with maternal fasting and post-challenge plasma glucose, while preterm delivery, hyperbilirubinaemia, and admission to NICU were related to post-challenge but not fasting glucose [238]. There was no association between perinatal mortality and maternal glucose levels, possibly reflecting the exclusion of 2.9% of women with raised glucose (1.7% with raised baseline two-hour glucose and 1.2% with raised random glucose later in pregnancy); nor was the

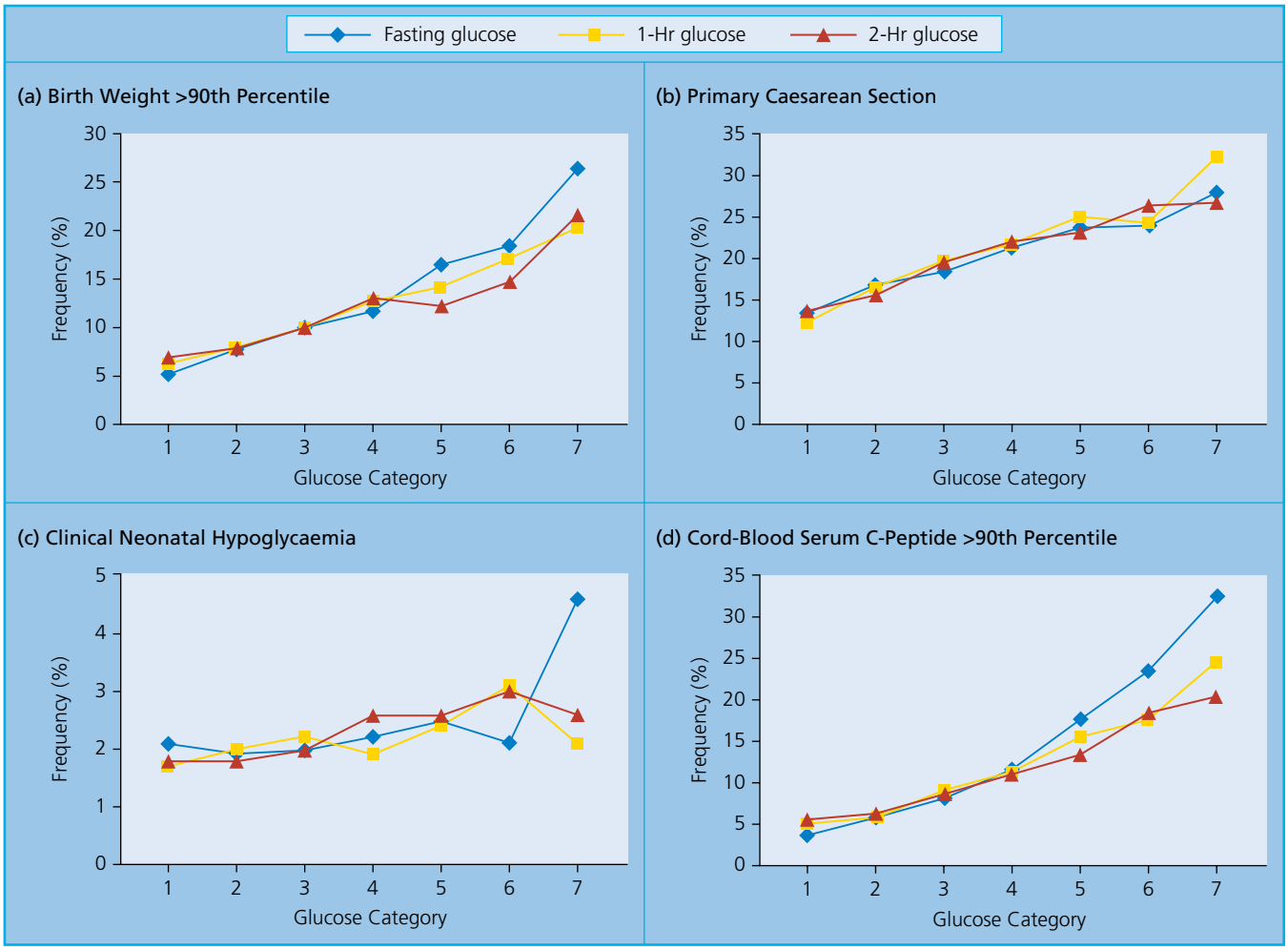


Figure 71.2 (a–d) Frequency of primary outcomes across the glucose categories. Glucose categories are defined as follows. Fasting plasma glucose level: category 1 <75 mg/dl (4.2 mmol/l); category 2 75–79 mg/dl (4.2–4.4 mmol/l); category 3 80–84 mg/dl (4.5–4.7 mmol/l); category 4 85–89 mg/dl (4.8–4.9 mmol/l); category 5 90–94 mg/dl (5.0–5.2 mmol/l); category 6 95–99 mg/dl (5.3–5.5 mmol/l); category 7 ≥100 mg/dl (5.6 mmol/l). One-hour plasma glucose level: category 1 <105 mg/dl (5.8 mmol/l); category 2 106–132 mg/dl (5.9–7.3 mmol/l); category 3 133–155 mg/dl (7.4–8.6 mmol/l); category 4 156–171 mg/dl (8.7–9.5 mmol/l); category 5 172–193 mg/dl (9.6–10.7 mmol/l); category 6 194–211 mg/dl (10.8–11.7 mmol/l); category 7 ≥212 mg/dl (11.8 mmol/l). Two-hour plasma glucose level: category 1 <90 mg/dl (5.0 mmol/l); category 2 91–108 mg/dl (5.1–6.0 mmol/l); category 3 109–125 mg/dl (6.1–6.9 mmol/l); category 4 126–139 mg/dl (7.0–7.7 mmol/l); category 5 140–157 mg/dl (7.8–8.7 mmol/l); category 6 158–177 mg/dl (8.8–9.8 mmol/l); category 7 ≥178 mg/dl (9.9 mmol/l). Source: Data from HAPO Study Cooperative Research Group 2008 [238].

HAPO study powered to detect such a relationship. More generally, it should be noted that there are no published studies that convincingly demonstrate a relationship between GDM and stillbirth or perinatal mortality [241].

A systematic review and meta-analysis of the association of hyperglycaemia and adverse perinatal outcomes [241], which included 25 reports of up to 207 172 women, reported a graded linear association between fasting and post-load concentrations across the whole glucose distribution. Most adverse perinatal outcomes occurred in women without pre-existing or gestational diabetes.

While demonstration of an association of hyperglycaemia with adverse outcomes is important, the key question is whether intervention confers clinical benefit. This was examined in two randomized controlled intervention trials involving around 1000 women with mild GDM: the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) [242] and the Maternal and Fetal Medicine Unit Network (MFMU) study [243]. In both trials women not meeting the diagnosis of diabetes outside of pregnancy were identified by a two-step diagnostic test, but with differing criteria for the two hours post-load glucose threshold, and randomized to treatment or no treatment (Table 71.10). Women in the MFMU trial had lesser degrees of hyperglycaemia, as reflected by the need for insulin, between the two studies (8% vs 20%). Both trials used composite endpoints because of the limited number of some clinical outcomes. Neither study reported the between-group differences in the blood glucose measurements achieved.

The composite primary outcome was reduced with treatment versus no treatment in ACHOIS (4% vs 1%); however, the biological plausibility of this result has been questioned, as the reduction was critically dependent on perinatal deaths: five deaths (1%) versus 0% in the routine care group, including a malformation and a case of severe growth retardation. In both trials, average birth weight, frequency of LGA, and pre-eclampsia were reduced by treatment (Table 71.10). The MFMU trial showed a reduction in caesarean section rate even though women were identified as having GDM. The frequencies of adverse outcomes in the untreated arms of these studies were similar to those found with maternal glycaemia above a putative threshold in the HAPO study.

A 2013 systematic review and meta-analysis of randomized trials for the US Preventive Services Task Force [244], dominated by these two trials, found that appropriate treatment of GDM (nutritional therapy supplemented by insulin if needed and self-blood glucose monitoring) versus routine care resulted in reductions in the following:

- Pre-eclampsia (RR 0.62; 95% CI 0.43 to 0.89; 7.2% vs 11.7%; three trials).
- Birthweight >4000 g (RR 0.50; 95% CI 0.35 to 0.71; five trials).
- Shoulder dystocia (RR 0.42; 95% CI 0.23 to 0.77; three trials).

More recent systematic reviews and meta-analyses have generally confirmed the benefit of treatment of GDM, including pharmacological therapy (primarily insulin and metformin), although most studies are small and variable in quality [245]. It is not always clear if observations are due to lower maternal glucose values or less maternal weight gain.

Based on these studies, consensus recommendations for the screening and diagnosis of hyperglycaemia in pregnancy were published by the IADPSG in 2010 [41] and subsequently endorsed by the WHO in 2013 [42] (Table 71.11). The diagnostic thresholds were met when the risk of adverse pregnancy outcomes (based on a composite of birth weight >90th centile, fetal fat, and cord blood

Table 71.10 Summary of key findings in the ACHOIS and MFMU trials.

	ACHOIS trial [242]				MFMU trial [243]			
Infant outcomes								
	Intervention group n = 506	**Control group n = 524**	**Adjusted RR**	**p value**	**Intervention group n = 485**	**Control group n = 473**	**Adjusted RR**	**p value**
Composite perinatal complication	7 (1%)	23 (4%)	0.33	0.01	149 (32.4%)	163 (37%)	0.87	0.14
Large for gestational age	68 (13%)	115 (22%)	0.62	<0.01	34/477 (7.1%)	66/454 (14.5%)	0.49	<0.01
Macrosomia	49 (10%)	110 (21%)	0.47	<0.01	28/477 (5.9%)	65/454 (14.3%)	0.41	<0.01
Shoulder dystocia	7 (1%)	16 (3%)	0.46	0.08	7/476 (1.5%)	18/455 (4.0%)	0.37	0.02
Neonatal nursery admission	357 (71%)	321 (61%)	1.13	0.01				
Jaundice	44 (9%)	48 (9%)	0.93	0.72				
Birth weight (g)					3301 ± 502.4	3408 ± 589.4		<0.01
Fat mass					427.0 ± 127.9	464.3 ± 222.3		<0.01
Maternal outcomes								
	Intervention group n = 490	**Control group n = 510**	**Adjusted RR**	**p value**	**Intervention group n = 476**	**Control group n = 455**	**Adjusted RR**	**p value**
Induction of labour	189 (39%)	150 (29%)	1.36	<0.01	130 (27.3%)	122 (26.8)	1.02	0.86
Caesarean delivery	152 (31%)	164 (32%)	0.73	0.98	128 (26.9%)	154 (33.8)	0.79	0.02
Pre-eclampsia					12 (2.5%)	25 (5.5%)	0.46	0.02
BMI at delivery (kg/m^2)					31.3 ± 5.2	32.3 ± 5.2		<0.01
Weight gain over trial period (kg)					2.8 ± 4.5	5.0 ± 3.3		

ACHOIS, Australian Carbohydrate Intolerance Study in Pregnant Women; BMI, body mass index; MFMU, Maternal and Fetal Medicine Unit; RR, relative risk.

Table 71.11 Recommendations for the diagnosis of hyperglycaemia in pregnancy and overt diabetes in pregnancy (International Association of Diabetes and Pregnancy Study Groups/World Health Organization criteria).

	Hyperglycaemia in pregnancy	Overt diabetes
	One or more of 75 g oral glucose tolerance test thresholds must be equalled or exceeded	
Fasting plasma glucose	≥5.1 mmol/l (≥92 mg/dl)	≥7.0 mmol/l (≥126 mg/dl)
	or	
1 h plasma glucose	≥10.0 mmol/l (≥180 mg/dl)	
	or	
2 h plasma glucose	≥8.5 mmol/ (≥153 mg/dl)	
HbA_{1c}		≥6.5%
Random plasma glucose[a]		≥11.1 mmol/l (≥200 mg/dl)

[a]A random plasma glucose to diagnose diabetes during early pregnancy should be confirmed by a fasting plasma glucose or glycated haemoglobin (HbA_{1c}).

Table 71.12 Early detection of hyperglycaemia in pregnancy (International Association of Diabetes and Pregnancy Study Groups/ World Health Organization criteria).

First prenatal visit	
Fasting plasma glucose, HbA_{1c}, or[a] random plasma glucose on all (or only on high-risk women)	If results are not diagnostic of overt diabetes, and a. Fasting plasma glucose ≥5.1 and <7 mmol/l (≥92 and <126 mg/dl), diagnose as hyperglycaemia in pregnancy b. Fasting plasma glucose <5.1 mmol/l (92 mg/dl), test for GDM at 24–28 weeks with 75 g oral glucose tolerance test[b]
24–28 weeks' gestation	
75 g oral glucose tolerance test after overnight fast	On all women not already diagnosed as hyperglycaemia in pregnancy or overt diabetes at first visit

GDM, gestational diabetes; HbA1c, glycated haemoglobin.
[a]A random plasma glucose to diagnose diabetes during early pregnancy should be confirmed by a fasting plasma glucose or HbA_{1c}.
[b]The 75 g oral glucose tolerance test thresholds represent the average value at which the odds for birth weight, percent body fat, and cord blood C-peptide (representing fetal insulin) exceeded 1.75 times the estimated odds of these outcomes compared with mean glucose values for the whole Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) population.

C-peptide) exceeded 1.75 of the estimated odds of these outcomes, compared with mean glucose values for the whole HAPO population. The recommendations distinguished overt diabetes from more minor degrees of glucose intolerance during pregnancy, and recommended screening for *overt diabetes* at the first prenatal visit, with diagnosis being based on non-pregnant criteria: fasting glucose ≥7 mmol/l or HbA_{1c} ≥48 mmol/l (6.5%) (Table 71.12).

Globally, the consensus recommendations have resulted in a much greater uniformity of approach to diagnosis than existed previously, but the thresholds remain the subject of active debate, particularly on issues relating to the increase in prevalence, methodology, logistics, medicalization of pregnancy, and cost-economic benefits [40, 246, 247] (Table 71.13).

For all HAPO participants, the prevalence of GDM (including women whose results were unblinded) was 17.8%, but varied from 9.3% (Israeli centre) to 25.5% (US centre) [255]. In most countries the thresholds have translated into a 2–3-fold increase in prevalence of GDM, up to 20–25%, and in some centres to 40% [249]. The appropriateness and validity of these increased rates have been questioned [245–247]. Most observational studies suggest that treatment of GDM defined by IADPSG criteria with high prevalence rates does not substantially reduce outcomes compared with older criteria giving a much lower population prevalence [253].

Methodological concerns relate largely to employment of a single OGTT glucose value, an arbitrary 1.75 risk threshold, and less robust clinical outcomes (birth weight, cord C-peptide, and neonatal skin folds being greater than the population 90% percentile), with RCTs showing only marginal benefit at these thresholds [253, 256–261]. Some would argue that a risk ratio of 2, as used in observational studies, rather than 1.75 would be more reliable [258], or indeed could be approximated if a high fasting glucose and one other raised threshold was used for diagnosis [262].

The thresholds have also been criticized for their potential *medicalization* of pregnancy and particularly in populations where IADPSG-defined thresholds are not associated with increased adverse outcomes [259–261]. Universal criteria defining GDM may both be wasteful and contribute to unnecessary anxiety [263].

The high IADPSG/WHO prevalence rates have been defended on the basis of their similarity to those in non-pregnant adults aged 20–44 years from the most recent US National Health and Nutrition Examination Survey (NHANES; 4.5% overt diabetes; 29.3% impaired glucose tolerance) [249, 250]. As the prevalence of undiagnosed diabetes is highest in this age group, even higher rates might be identified if systematic prepregnancy testing was instituted effectively. In addition, comprehensive gluco-metabolic antenatal screening would help identify both lipid and glucose abnormalities present many years before pregnancy testing [251]. The recent decision to reduce screening of young adults to 35 years is unprecedented and provides further support for the GDM prevalence rates [252].

Although the majority of women in HAPO with adverse outcomes had glucose levels below the thresholds, some of these women may have had one or two values equalling or exceeding the IADPSG thresholds. In addition, other data have shown the importance of even a single abnormal threshold value for prediction of future GDM. While the original HAPO study focused on short-term outcomes, the significant impact of these thresholds for adverse metabolic and cardiovascular outcomes in both mother and offspring has been shown in the long-term follow-up and needs to be incorporated into cost-economic models of care. The majority of women with GDM are managed by diet alone, thus minimizing medical intervention [242, 243]. It has been acknowledged that the IADPSG diagnostic thresholds are not applicable to early pregnancy, and indeed the value of earlier diagnosis of GDM during pregnancy, and by what criteria, is the subject of active research.

Screening strategies and glucose thresholds vary across different countries [5, 15, 40, 60, 179–181, 234] in the use of a preliminary screening test, glucose load, number of glucose values that must be equalled or exceeded, and glycaemic thresholds (Table 71.14). The IADPSG [60] and New Zealand criteria [181] advise early detection by random plasma glucose and HbA_{1c},

Table 71.13 Concerns and comments about the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria for gestational diabetes mellitus (GDM) [41].

Basic issue	Specific concern	Comment
Diagnosis of GDM in early pregnancy	IADPSG recommends screening by blood test in first trimester using same diagnostic thresholds as derived from testing in late second trimester [238]	Most international bodies (although not NICE [15]) endorse screening in first trimester with blood test for undiagnosed type 2 diabetes General agreement that IADPSG thresholds should not apply to early pregnancy [248]
Prevalence	2–3-fold increase in prevalence rates	Potential for overdiagnosis and affordability issues, but supported by high prevalence of women with prediabetes in this age group outside pregnancy [249–252]
Methodology	Single OGTT Arbitrary 1.75 glucose threshold Less robust clinical outcomes	Variability and poor reproducibility of OGTT glucose IADPSG 1.75 risk ratio regarded as too low [246] and lack of RCT data for reliability [253] Preference for more robust and clinically meaningful outcomes Supported by high prevalence rates outside pregnancy and adverse long-term data in mother and offspring [254]
Logistics	Increasing number of individuals with diabetes	Management issues with diversion of resources from pregestational diabetes, but can be addressed by strategies such as algorithm-guided management of low-risk individuals
Medicalization	Pregnancies previously considered healthy now given a label with greater medical input and potentially greater intervention, irrespective of glycaemia and fetal growth	Identification of women with GDM who are not at risk of adverse outcomes has psychological and economic consequences [253], but majority of these women can be treated with diet alone
Cost economics	Conflicting cost-economic data Some diagnostic criteria derived largely from cost-economic models with different thresholds [15] Modelling suggests criteria are only cost-effective if caesarean section or maternal diabetes can be prevented	Cost-economic datasets based on non-selected populations, some of which are not blinded, and do not take account of adverse long-term maternal/fetal outcome data

NICE, National Institute for Health and Care Excellence; OGTT, oral glucose tolerance test; RCT, randomized controlled trial.

respectively, while in the UK [15], Canada [180], and USA [60], testing is recommended only if risk factors are present. Screening strategies include selective screening (UK NICE [15]) with testing at 24–28 weeks based on risk factors, universal screening using a two-step approach in the USA (ADA and American College of Obstetrics and Gynecology [AOCG] [60, 234]) and Canada [180], and universal screening using a one-step strategy in countries with high-risk and low–medium-risk populations [264]. In many low-resource settings (e.g. sub-Saharan Africa) testing is not routinely available, partly because the OGTT is cumbersome and labour intensive. Consequently, the International Federation of Gynecology and Obstetrics (FIGO), while supporting WHO/IADPSG criteria with universal biochemical testing, acknowledged that adaptation might be needed across countries to reflect variation in the balance of undiagnosed GDM [40, 249] with access to and quality of laboratory glucose and HbA_{1c} measurement. ACOG opted to retain the two-stage process involving a 50 g glucose challenge test followed by a 100 g OGTT [234], while ADA [60] allows for either the single-stage IADPSG or two-stage method with differing criteria.

By contrast, NICE [15], utilizing a cohort of 40 000 pregnant women, recommended substantially different thresholds based on a cost-economic analysis (fasting ≥5.6 mmol/l [101 mg/dl] and two hours ≥7.8 mmol/l [140 mg/dl]) among a subset of 18 974 women for whom fasting, one-hour, and two-hour glucose values were available. Uncertainties surrounding the validity of these analyses have been highlighted, however, given that 12 000 of these women had undergone universal screening and that the cost-effectiveness of selective versus universal screening depends on the prevalence of GDM within an individual community [265]. The NICE two-hour threshold is much lower than the other guidelines and the concordance of the fasting and two-hour UK diagnostic thresholds was estimated to be as low as 55%. Other groups have suggested that lower thresholds would be more appropriate for different ethnic groups [259].

Overt diabetes during pregnancy

The IADPSG [41], WHO [42], and later FIGO [40, 249] distinguished GDM from *overt diabetes in pregnancy* (defined by non-pregnant thresholds of fasting glucose ≥7.0 mmol/l [126 mg/dl] or two hours ≥11.1 mmol/l [200 mg/dl]) (Table 71.11). The presumption is that women with more severe degrees of hyperglycaemia (including prepregnancy) would be at greater diabetic and obstetric risk (including malformations), and in turn merit more careful vigilance and intensive management. It is noteworthy that such women, for ethical reasons, were excluded from the HAPO study, thus potentially reducing some of the adverse outcomes. Similar exclusions were also applied to the ACHOIS and MFMU studies [242, 243].

GDM: disease entity or risk factor?

The continuous relationship between glucose and adverse outcomes has been viewed by some to be more analogous with the relationship between blood pressure or cholesterol and ischaemic heart disease [181, 246]. Maternal glucose is considered to be one of

Table 71.14 Screening and testing approaches recommended by international diabetes organizations.

Organization	Screening and testing approach	Risk factors used (if any)	Diagnostic method
NICE [15]	Offer women with risk factors OGTT at 24–28 weeks Offer women with previous GDM early capillary glucose monitoring *or* early pregnancy OGTT	BMI ≥30 kg/m^2 High-risk ethnicity First-degree relative with diabetes Previous macrosomia (≥4.5 kg) Previous GDM	2 h 75 g OGTT
Endocrine Society [179]	Test all women using fasting plasma glucose, HbA_{1c}, or an untimed random plasma glucose at the first prenatal visit Those testing negative should undergo repeat testing for GDM at 24–28 weeks	None	2 h 75 g OGTT
ADA [60]	Test women with risk factors at initial visit (to screen for overt diabetes) by HbA_{1c}, fasting glucose, random glucose, or 75 g OGTT Retest those testing negative along with all other women at 24–28 weeks	BMI ≥25 kg/m^2 plus one or more of: First-degree relative with diabetes High-risk ethnicity History of CVD or hypertension HDL cholesterol <0.9 mmol/l Triglyceride >2.82 mmol/l PCOS Physical inactivity	50 g GCT followed by 3 h 100 g OGTT in those GCT positive *or* 2 h 75 g OGTT
ADIPS [181]	Test women with risk factors at first antenatal visit, ideally by OGTT or HbA_{1c} Retest those with normal results, along with all other women, at 24–28 weeks	Previous GDM Previous hyperglycaemia Age ≥40 yr High-risk ethnicity First-degree relative with diabetes BMI ≥30 kg/m^2 Previous macrosomia (4.5 kg or >90th centile) PCOS Steroid or antipsychotic use	2 h 75 g OGTT
Diabetes Canada [180]	Test women with risk factors at first antenatal visit for overt diabetes using HbA_{1c}, FPG, or OGTT Retest those testing negative, along with all other women, at 24–28 weeks	Age ≥35 yr High-risk ethnicity Corticosteroid use BMI ≥30 kg/m^2 Previous GDM Pre-diabetes Previous infant >4 kg PCOS Parent or sibling with type 2 diabetes	50 g GCT followed by 2 h 75 g OGTT in those GCT positive (preferred) *or* 2 h 75 g OGTT alone

ADA, American Diabetes Association; ADIPS, Australasian Diabetes in Pregnancy Society; BMI, body mass index; CVD, cardiovascular disease; FPG, fasting plasma glucose; GCT, glucose challenge test; GDM, gestational diabetes mellitus; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; NICE, National Institute for Health and Care Excellence; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome.

several risk factors, the detection and treatment of which may vary depending on the presence of other risk factors or only if a particular diagnostic or treatment threshold is exceeded. This approach also focuses attention on the outcome of interest, quantification of the risk, relevant risk factors, and a targeted approach to intervention and the tangible benefits of treatment.

At one end of the spectrum are women with previously undiagnosed diabetes at risk of malformations and perinatal mortality, who clearly merit treatment, while at the other end of the spectrum the risk is primarily that of excess fetal growth [238], which may be viewed as a risk factor for adverse outcomes rather than a disease *per se* [258]. Not all women with GDM are at significant risk and only a minority will benefit from treatment [253].

With the possible exception of South Asian women [234], this approach has not been adopted for GDM, although various risk engines have been examined [266]. Equally, some have expressed a preference for the term *hyperglycaemia in pregnancy* [267], which may help in the conceptualization of risk or in glucose being viewed as one of a number of risk factors, with the potential to reduce the medicalization of pregnancy.

Diagnosis in the first trimester (timing of screening)

Traditionally, with the exception of women known to have previous GDM, screening for GDM has been targeted at 24–28 weeks' gestation due to the development of insulin resistance in the later part of pregnancy [15, 40, 60, 232]. It has also been acknowledged that the IADPSG thresholds are applicable only to diagnosis at 24–32 weeks' gestation (average 28 weeks), and cannot simply be extrapolated to early pregnancy [41, 248] given the changes in glucose metabolism with gestation. NICE guidelines advise against plasma glucose or

HbA_{1c} testing early in pregnancy, even to rule out pre-existing type 2 diabetes, because of the scarcity of cost-effectiveness studies [15].

The case for early identification of GDM [268] is supported by a study showing that diagnosis after 28 weeks' gestation is already accompanied by a twofold higher risk of fetal abdominal circumference >90th centile (OR 2.05), which increases further (OR 4.52) when combined with maternal obesity [269], and ultimately is associated with a fourfold increase in the risk of being born LGA. Moreover, in a large multiracial prospective cohort study, initial acceleration of fetal growth and accrual of fast mass were detectable at 20 weeks' gestation [270]. In India, elevated fetal adiposity was noted before the diagnosis of GDM in women who did not have pre-diabetes or type 2 diabetes in early pregnancy [271]. Offspring of these women had higher adiposity, but did not have an elevated birth weight (the *thin–fat phenotype*).

The onset of gestational diabetes might occur as early as 16–20 weeks' gestation, and earlier maternal hyperglycaemia [272] and fetal hyperinsulinaemia (14–20 weeks) [273] are associated with later development of GDM and LGA babies. Observational studies have shown that fasting glucose (across the normal range up to 5.8 mmol/l [105 mg/dl]) in the first trimester is predictive of later GDM, LGA, and caesarean section [272]. Women with GDM diagnosed in the first trimester (by Carpenter–Coustan criteria) have increased rates of hypertension and pre-eclampsia compared with a later diagnosis [274], with a suggestion (albeit limited by small numbers) of increased rates of neonatal hypoglycaemia and perinatal mortality [275]. Women with GDM and higher HbA_{1c} at diagnosis (41–49 mmol/l [5.9–6.6%]) had increased rates of adverse outcomes (pre-eclampsia and preterm birth], and rates of pre-eclampsia were reduced in a subgroup who were diagnosed and treated before 24 weeks compared with those who began treatment later [276].

A meta-analysis that examined screening for early-onset GDM found that 15–70% of cases could be detected before 24 weeks' gestation [277], while the overall prevalence of early GDM ranged from 0.8% to 22.9% across studies. Although the wide range reflects differing screening methodologies and diagnostic criteria, a considerable proportion of GDM may develop in early gestation and remain undiagnosed under current guidelines. In the meta-analysis, women diagnosed with GDM <24 weeks compared with those diagnosed later had a higher risk of perinatal mortality (RR 3.58), neonatal hypoglycaemia (RR 1.61), and insulin use (RR 1.71). A recent retrospective analysis compared women diagnosed with GDM <24 weeks with those diagnosed >24 weeks in 1471 pregnancies [278] and reported that despite treatment, women diagnosed earlier in pregnancy had significantly higher rates of pregnancy-induced hypertension, postpartum haemorrhage, and need for caesarean section. The offspring meanwhile had higher rates of macrosomia, prematurity, stillbirth, and need for neonatal intensive care.

Women who develop GDM in early pregnancy are more likely to be older, multiparous, with a higher BMI and a family history of type 2 diabetes [277]. In addition, uptake of OGTT in early pregnancy is apparently poor, and in one large prospective study only 23.2% took advantage of the offer of testing [279]. Fasting plasma glucose alone may be more practical in early pregnancy, although a large Chinese cohort of 17 186 pregnancies found that only 37% of women with FPG ≥5.1 mmol/l in the first trimester had a positive OGTT at 24–28 weeks [280]. Furthermore, given the changes in glucose metabolism through pregnancy, expert consensus on the diagnostic thresholds for early pregnancy is lacking [248].

While early identification of GDM might allow more timely intervention, more substantive cohorts comparing various risk factors together with dedicated RCTs in early pregnancy are needed, with the important exclusion of women at high likelihood of diabetes before pregnancy, whether defined by impaired fasting glucose (6.0–6.9 mmol/l) or by HbA_{1c} (6–6.5%). An ongoing RCT involving the identification of women with GDM using an OGTT in early pregnancy (<20 weeks) will provide important information regarding whether or not early intervention can improve pregnancy outcomes [281].

Screening tests

Two-step test

The 50 g glucose screening test (GST) involves a blood glucose test before and one hour after a non-fasting 50 g glucose load, followed, if positive, by a diagnostic OGTT. Traditionally in the USA this was endorsed either as the method of choice or, following the IADPSG recommendations, as one of two valid methods of testing for GDM [60]. The non-fasting nature of the test offers convenience, but its greater complexity (scheduling issues, inconvenience, and cost) was associated with poorer uptake of the second visit, even in well-resourced countries such as Canada [282]. This is likely to be greatly magnified in lower- and middle-income countries, resulting in the majority of at-risk pregnancies effectively being untested and leading to missed follow-up opportunities. Other concerns are the poor sensitivity, specificity [283], and reproducibility [284] of post-glucose screening tests.

The two-step strategy misses ~25% of women who would be diagnosed by a full OGTT [282]. Those with a positive screen may modify their lifestyle and other factors prior to their diagnostic OGTT, which may also account for some of the difference in prevalence. The two-step approach fails to identify women primarily manifesting fasting hyperglycaemia, as they do not qualify for the OGTT. In the HAPO study, the frequency of GDM diagnosed by fasting glucose ranged from 24% to 26% in Thailand and Hong Kong to 73–74% in the USA and the Caribbean [253]. The two-step test may therefore miss many women with hyperglycaemia in pregnancy.

One-step universal approach

The one-step universal test offers a single diagnostic OGTT. Given the variability in results due to clinical, pre-analytical, and analytical factors [285, 286], this may result in a differing diagnostic classification on repeat testing; however, the initial dietary nature of any intervention would favour this drawback over failing to detect significant maternal metabolic risk. The poor reproducibility of the GST has also been highlighted [286]. A recent USA-based systematic review found that women with one abnormal value on their diagnostic three-hour OGTT are at substantially higher risk of LGA babies, caesarean delivery, hypertension, Apgar score less than 7, NICU admission, and respiratory distress syndrome [287]. The one-step approach is associated with better perinatal outcomes [288]. For these reasons, it would seem unwise to revert to a two-step approach for such large populations.

A recent US pragmatic RCT by Hillier et al. [289] involving 23 792 predominantly white and Asian women from two Kaiser Permanente health systems identified 16.5% of women using a one-step diagnostic process (75 g OGTT interpreted by IADPSG

criteria) and 8.5% using a two-step process as described earlier. The results showed no maternal or perinatal benefit overall between the two screening strategies [290]. In a responsive commentary, McIntyre et al. [291] highlighted that the lack of effect at a population level was to be anticipated, as 92% of women in each arm were treated in a similar manner and the small reduction in LGA frequency with a one-step versus two-step approach (8.9% vs 9.2%) is consistent with predictions from previous studies [292]. In addition, the Hiller study was integrated into standard care and allowed providers the option of using a diagnostic strategy of their own choice rather than the random allocation (only 66% of women in the one-step group received their allocated testing strategy, compared with 92% in the two-step group), which, although controlled for, raised the possibility of residual bias. Although the one-step approach almost doubled the GDM frequency, it identified women with an almost equal risk of having hyperglycaemia severe enough to merit pharmacotherapy (43% with the one-step and 46% with the two-step method). While outcomes did not differ at a population level, the study was unable to address whether the additional 8% of women diagnosed with GDM using the one-step approach would have derived benefit from treatment [291].

Fasting plasma glucose screening test

Fasting glucose concentrations reach a nadir around the 12th week of pregnancy and then stay relatively constant for the remainder of pregnancy [293]. FPG as a screening test is attractive because it is relatively easy to obtain, well tolerated, reproducible, and inexpensive [293]. Interpretation of studies using FPG, however, is made difficult by the employment of FPG as a screening test (which may enhance sensitivity and assumes 100% reproducibility, which is unlikely to be the case), different glucose loads, and variation in thresholds to be equalled or exceeded for diagnosis [294]. In two studies, using the Carpenter–Coustan and WHO criteria, respectively [295, 296], similar sensitivities (81% and 88%) and specificities (76% and 72%) were found at a FPG threshold of 4.8 mmol/l (86 mg/dl). By contrast, two studies that utilized IADPSG diagnostic criteria reported sensitivities of 92.5% and 74%, respectively [297, 298], at an FPG threshold of 4.7 mmol/l (85 mg/dl). Two studies using FPG as a first screening test for GDM diagnosed in early third trimester by IADPG criteria at an FPG threshold of 5.1 mmol/l (92 mg/dl) reported sensitivities of 27% [299] and 26% [300], with respective specificities of 95% and 90%, suggesting that until further data are available, FPG should not be used for screening purposes in the first trimester.

Glycated haemoglobin as a screening test

When used as a screening test, regardless of when the test is done, the higher the HbA_{1c}, the more likely the diagnosis of GDM [293]; however, there is a marked overlap in values between women with and without GDM, thus limiting its value [301]. In several studies in which all women received diagnostic testing for GDM using a threshold of 5.4–5.7% (35–48 mmol/mol), sensitivities varied from 26% to 86% and specificities from 21% to 92% [293]. A large (n = 8497) study examined HbA_{1c} as a screening test at the first prenatal visit (median 47 d) for the diagnosis of GDM in later pregnancy defined by IADPSG criteria. In the study 82% of the 692 women diagnosed with GDM had an HbA_{1c} result <5.9% (41 mmol/mol) and 23% of GDM was diagnosed prior to 20 weeks; the remaining 77% was discovered either on initial or repeat OGTT testing after 20 weeks. Only 5% of 8497 women who underwent HbA_{1c} screening proceeded to undertake the OGTT [279].

Selective versus universal screening

Approaches to GDM detection vary widely (Table 71.14). Those international bodies that advocate universal screening do so based on the high prevalence rates of GDM [302], the generally asymptomatic nature of GDM, and the association of hyperglycaemia with adverse pregnancy outcomes independent of other risk factors.

Risk factor–based screening is the selection of women with such risk factors to undergo formal testing for GDM. Women with one or more clinical or obstetric risk factors are generally at high risk of GDM [293, 303]. NICE has defined five such factors: family history in a first-degree relative, BMI >30 kg/m^2, previous big baby (>4.5 kg), previous GDM, and belonging to certain ethnic groups (e.g. from Latin America, Africa, Pacific Islands, Southeast Asia, or the Asian subcontinent) [15]. Other risk factors include maternal age (e.g. ≥30 yr) and increased parity [15, 285]. Certain risk factors (e.g. previous GDM) have greater positive predictive value, while others (previous GDM, previous macrosomia) create a bias for parity to be a risk factor. The greater the number of risk factors, the greater the positive predictive value for GDM [293]. Risk factors are only around 50% sensitive and specific for GDM, meaning that some women with GDM will only be identified through universal testing, regardless of how risk is defined. In a recent systematic review and meta-analysis assessing the performance of risk factor screening, there was no superior combination [303]. Approximately 70% of women would need to undergo testing to identify 80% of cases of GDM, and all women would need to undergo testing to achieve a sensitivity above 90%. Across studies, the NICE criteria had a sensitivity of 78.2% and specificity of 31.7%; overall, 67.2% of women would require OGTT employing NICE screening criteria [15]. The NICE recommendation is based largely on cost-economic considerations, although in another UK report GDM screening was cost-effective if the population GDM frequency was greater than 4.2% [265].

Poor compliance rates with risk factor–based protocols, together with the inconvenience and non-compliance with return for non-diagnostic testing [40], would also favour a universal approach [253]. Alternatively, FIGO has suggested pragmatic approaches [249] to accommodate differing country and healthcare systems. In individual populations and in countries where IADPSG-defined OGTT thresholds are not associated with adverse outcomes, treatment at different glycaemic thresholds may be needed to achieve comparable outcomes [261]. A global consensus for GDM diagnosis may remain the ideal [291].

Risk engine

The fact that pregnancy outcomes relate to multiple risk factors has generated interest in whether a *risk engine* approach might give a more comprehensive appreciation of the relationship between maternal demographic and biological risk factors and adverse pregnancy outcomes [266], especially where the prevalence of maternal obesity is high and its effects on pregnancy complications may predominate [304]. The development of personalized composite risk scores may optimize the benefits of antenatal intervention, but there is a need to recognize differential risk among ethnic groups [234], or relative risk contributions by differential predictors for outcomes of GDM or its complications [305]. In addition, the current strategy does not reflect the pathogenesis of GDM, which is likely to be heterogeneous [306–308] and might further help identify those women who would benefit the most from

continuing monitoring and intervention. Prediction of GDM is likely to be facilitated by integrating healthcare databases containing relevant clinical and biochemical variables, while targeting resources to those most in need in low- and middle-income countries [305].

Cost-effectiveness of screening

Relevant issues include the costs and benefits of treatment of GDM and the cost and risk of those who have the disease but with a negative screening result. Cost models will differ depending on whether the outcomes are confined to more physiological endpoints, such as LGA, or more adverse maternal and fetal outcomes. Most models have not factored in long-term health outcomes.

Two previous large RCTs showed benefit from treatment of GDM [257, 258]. Each of these studies employed different glucose loads, different numbers of elevated OGTT results, and different glycaemic thresholds from IADPSG to define GDM, as well as different thresholds to initiate insulin treatment. More recent studies comparing IADPSG with traditional thresholds have not shown improvements in treatment, and some have compared one-step versus two-step diagnostic approaches rather than the cost-effectiveness of IADPSG thresholds [249].

Studies on the cost-effectiveness of GDM screening strategies and diagnostic criteria are limited [309–311]. Using a quality-adjusted life year, one study determined that no cost-effective screening was indicated for populations where the risk was <1%, while for those with a risk of >4.2% a universal OGTT was the most cost-effective [265]. Two studies concluded that testing with the new IADPSG criteria was expensive but cost-effective [312, 313], while other studies [260] did not find it cost-effective.

While the focus has been largely on immediate pregnancy outcomes, much of the personal and public health *value* of GDM detection lies in the opportunity to identify women who carry long-term risk of developing overt diabetes, cardiovascular disease, and premature mortality [254, 314–319]. Future cost-economic modelling of various diagnostic thresholds and screening and preventive strategies must include both short- and long-term outcomes [320, 321] together with consideration of more specific analysis pertaining to particular populations and low-income settings [322].

Management of gestational diabetes

Management and glycaemic targets advised by international bodies are shown in Table 71.5. NICE glucose targets (fasting <5.3 mmol/l, one-hour post-prandial <7.8 mmol/l, and two-hour post-prandial glucose <6.7 mmol/l) are similar to those of diabetes preceding pregnancy. FPG levels of ≥5.8 mmol/l are associated with an increased risk of preventable perinatal complications [99] and are thus an indicator that pharmacological treatment is likely to be of benefit. NICE recommends that women with a fasting blood glucose level of ≥7.0 mmol/l at diagnosis of GDM should be treated with insulin in preference to oral diabetes drugs [15].

Treatment of mild hyperglycaemia reduces fetal growth and the proportion of infants born LGA, but it is unclear whether infants who are small or appropriate for gestational age benefit from treatment. In an elegant study, Hispanic women with mild hyperglycaemia (fasting glucose <5.8 mmol/l) and fetal abdominal circumference greater than the 75th centile were randomized to diet therapy alone (29 women) or diet with twice-daily insulin (30 women), with target fasting glucose of 4.4 mmol/l and two-hour post-prandial <6.1 mmol/l. The LGA rate in the diet-treated group was 45%, significantly greater than the insulin-treated group (13%), and the diet-treated group had an initial abdominal circumference <75th centile (14%) [99]. There remains the possibility of overtreatment producing growth-retarded babies.

Diet and lifestyle modification

Women with GDM require education and individualized nutritional advice [323, 324]. The food plan should provide adequate calorie intake to promote fetal growth and maternal health, achieve glycaemic goals, and promote weight gain according to 2009 Institute of Medicine recommendations [213]. There is no definitive research to specify an optimal calorie intake for women with GDM or determine whether calorie needs differ from those of pregnant women without GDM. The key principles are to reduce overall energy intake and limit the proportion derived from carbohydrates. Simple carbohydrates result in higher post-meal glucose excursions than more complex carbohydrates. Recognized dietary modifications to lower blood glucose levels include reducing caloric intake for women with overweight and obesity (e.g. to ~25 kcal/kg body weight), limiting carbohydrate to 35–40% of total calories, and utilizing carbohydrate foods with a low glycaemic index. The Dietary Reference Intakes for all pregnant women recommend a minimum of 175 g carbohydrate, 71 g protein, and 28 g fibre. The diet should emphasize monounsaturated and polyunsaturated fats while limiting saturated fats and avoiding trans fats. Regular exercise is often recommended and there is limited evidence that it reduces fetal birth weight [325].

Self-monitoring of blood glucose (fasting and one-hour post meals) provides early warning of progressive hyperglycaemia and the need for additional therapy, especially if associated with accelerated fetal growth. Lifestyle change is sufficient to control hyperglycaemia in 80–90% of women [242, 243]. Women treated with diet alone are usually at lower risk and logistically might be managed in a less intense setting using a treatment algorithm.

Pharmacological treatment

Insulin

If diet and exercise are insufficient to manage maternal hyperglycaemia, insulin is an effective treatment to prevent fetal complications, especially those related to fetal overgrowth. It is tailored to glycaemic targets and preferred by some international bodies as the mainstay of treatment because it does not cross the placenta [60]. The goals of treatment (including reduction of post-prandial hyperglycaemia) are similar to those for type 1 diabetes and multiple-daily insulin regimens are frequently used. The starting dose of insulin is 0.1 unit/kg/d and with expert advice can easily be commenced as an outpatient with active titration. Both twice-daily and multiple-daily insulin injections are reasonable delivery strategies and neither has been shown to be superior to the other during pregnancy [326].

There are some women with GDM requiring medical therapy who, due to cost, language barriers, comprehension, or cultural influences, may be unable to use insulin safely. Oral agents may be an alternative in these women after a discussion of the known risks and the need for more long-term safety data in the offspring.

Metformin

In the largest trial [327], 751 Australian women with GDM at 20–33 weeks' gestation were randomized to metformin (1000–2000 mg daily), with insulin supplementation if needed, or insulin. Perinatal morbidity (composite outcome) was similar in the two groups (32.0% vs 32.2%, respectively). Severe neonatal hypoglycaemia (<1.6 mmol/l) was lower with metformin (3.3% vs 8.1%; p = 0.008), but preterm birth was more common (12.1% vs 7.6%; p = 0.04). Maternal weight gain was lower in the metformin group (0.4 vs 2.0 kg; p = 0.001). Glycaemic levels were similar between the groups, although 46.3% of women in the metformin group required insulin.

Seven subsequent smaller trials largely confirmed the safety and efficacy of metformin in GDM compared with insulin [328], while three trials comparing metformin with glibenclamide suggested less maternal weight gain, lower birth weights, and higher neonatal blood glucose levels. In most of these trials, approximately half of metformin-treated women required insulin. These women were generally older with higher baseline BMI, more marked and earlier hyperglycaemia, and earlier diagnosis and treatment of GDM. In systematic reviews, metformin was associated with a lower risk of neonatal hypoglycaemia and less maternal weight gain than insulin [260, 329–333].

Metformin readily crosses the placenta, resulting in umbilical cord blood levels of metformin as high as or higher than simultaneous maternal levels [60]. In a follow up of 7–9-year-old offspring in the Metformin in Gestational diabetes study (MiG-TOFU), offspring exposed to metformin compared with insulin in one cohort were heavier and had a higher waist-to-hip ratio and waist circumference [334]. In two RCTs of metformin use in pregnancy for polycystic ovary syndrome (PCOS), follow-up of 4-year-old offspring exposed to metformin had higher BMI and increased obesity, while at 5–10 years exposed offspring had higher BMI, waist-to-hip ratio, and waist circumference, and a borderline increase in fat mass [335]. A recent meta-analysis concluded that metformin exposure resulted in smaller neonates with acceleration of postnatal growth resulting in higher BMI in childhood [336]. Other follow-up trials are currently in progress. Due to the potential for growth restriction or acidosis in the setting of placental insufficiency, metformin should not be used in women with hypertension or pre-eclampsia or those at risk for IUGR [60].

UK NICE guidelines approve the use of metformin to treat GDM after appropriate discussion of the benefits and risks [15]. Rapid dose escalation and early commencement of insulin (possibly even concurrently with metformin) are advised to minimize the duration of hyperglycaemia in women with high BMI, previous GDM, and high baseline glucose, suggesting likely failure with metformin as a single agent. ADA guidance recommends the substitution of insulin [60] because it crosses the placenta and has limited efficacy.

Sulfonylureas

The only large randomized trial of glibenclamide (glyburide) [337] involved randomization of 404 women with fasting hyperglycaemia despite diet at 11–33 weeks' gestation to insulin or glibenclamide therapy (2.5–20 mg daily). Glycaemic levels and neonatal outcomes were similar between the two groups. In the glibenclamide group, 4% needed insulin. Subsequently four small RCTs comparing glibenclamide with insulin reported an increased rate of neonatal hypoglycaemia, macrosomia, and IUGR [332, 333, 338]. Other retrospective observational studies have generally confirmed the effectiveness of glibenclamide, but variously reported increased rates of pre-eclampsia, macrosomia, lower ponderal index, lower Apgar scores, the need for phototherapy, neonatal hypoglycaemia, stillbirth (in those treated early in gestation), and NICU admission. Approximately 20% of women treated with glibenclamide needed to be switched to insulin [328].

Sulfonylureas cross the placenta and concentrations of glibenclamide in umbilical cord plasma are approximately 50–70% of maternal levels [60, 339]. In a meta-analysis and systematic review in 2015 [329], glibenclamide was associated with a higher rate of neonatal hypoglycaemia and macrosomia than insulin or metformin. More recently, glibenclamide failed a non-inferiority test compared with insulin based on a composite outcome of neonatal hypoglycaemia, macrosomia, and hyperbilirubinaemia [340]. Long-term safety data for offspring exposed to glibenclamide are not available. Furthermore, glibenclamide failed to provide adequate glycaemic levels in 23% of women with GDM [341]. No international body approves the use of glibenclamide during pregnancy.

Delivery

The UK NICE guidelines recommend that women with GDM treated with tablets or insulin should be delivered before 40 weeks' gestation [15], but in practice obstetricians make a decision based on individual risk. Delivery guidelines are similar to those for diabetes preceding pregnancy, particularly for women on insulin. In general, glycaemic management during delivery does not require such intense monitoring or a glucose infusion.

Postpartum management

Post-delivery, any pharmacological treatment started during pregnancy is discontinued in anticipation that the woman will revert to normal glucose tolerance. This can be established provisionally using capillary glucose monitoring before leaving hospital, but should be confirmed by formal postnatal testing. Traditionally, the latter involved an OGTT test around six weeks post-delivery, although uptake rates of only around 23–58% are reported [15].

GDM is a risk factor for subsequent GDM [342], type 2 diabetes [343, 344], the metabolic syndrome [345, 346], and increased cardiovascular risk [315–319] compared to women without GDM. Women with GDM diagnosed during pregnancy need to have repeat testing postnatally for the early detection of previously unrecognized type 2 diabetes or pre-diabetes, and, if suspected, formal exclusion of type 1 diabetes and genetic types of diabetes. The postnatal visit also provides a unique opportunity to offer lifestyle advice, screen for cardiovascular risk factors, and remind women of the need for regular contraception and early referral in the eventuality of future pregnancy. A simple gestational recall register or an appointment with a dedicated cardiovascular coordinator might improve the follow-up of women with gestational diabetes [347]. Despite this evidence, only half (58%) of women in the UK in the first year after a GDM pregnancy underwent any glucose testing and even fewer had a lipid test [316]. Although the risk of incident type 2 diabetes is recognized, and previous history of gestational diabetes is incorporated into the QDiabetes-2018 risk prediction algorithm [348], this information has not been incorporated into cardiovascular disease risk calculators.

Various social and medical risk factors for non-attendance for postnatal screening have been identified. Women who missed testing were at a high risk of cardiovascular disease [349]. FPG is conceivably a simpler and cheaper alternative, but the need for an overnight fast may present difficulties to mothers with young children. Limitations of HbA_{1c} relate to increased red blood cell

turnover in pregnancy and blood loss at delivery, although in its favour are the convenience of a single non-fasting blood test, higher pre-analytical stability, ease of repetition, and availability of point-of-care testing, especially in resource-limited settings. The OGTT is more sensitive at detecting glucose intolerance (including both diabetes and pre-diabetes), although these comparisons are in relation to the OGTT as the gold standard rather than independent outcomes [349].

Most international bodies continue to recommend postnatal OGTT testing [60, 180, 181]. By contrast, the NICE 2015 guidelines recommend either a fasting plasma glucose (FPG) or HbA_{1c} at least 13 weeks after delivery rather than OGTT testing for postpartum screening [15]. All women with GDM, irrespective of postnatal glycaemic status, should be counselled that their lifetime risk of diabetes is higher than the rest of the population and offered lifestyle interventions, similar to people with impaired glucose tolerance. High-risk groups (e.g. certain ethnic minorities, those with overweight or obesity, women diagnosed early in pregnancy) should be specifically targeted for intervention strategies. Those with normal or impaired glucose tolerance postnatally should have ongoing surveillance by annual fasting glucose or HbA_{1c} every 1–3 years [15, 60], along with continuing lifestyle education and monitoring of cardiovascular risk factors. Follow-up plans are often poor, as these women fall between primary and secondary care teams and no international guidelines recommend screening for other cardiovascular risk factors.

Maternal obesity

The increasing prevalence of obesity in women of reproductive age is being translated into pregnancy [350, 351] and is projected to increase further [352]. In 2011–2014, 34% of US women aged 20–39 years had obesity (57% among Hispanic Black women [353]), while among live births in 2015, 26% of women had obesity prepregnancy and another 26% were overweight [354]. Maternal obesity and gestational weight gain can be viewed as important factors in fetal overnutrition and, together with a reduction in cigarette smoking, largely explain the trend to increasing birth weight [355].

Pregnant women with obesity are at increased risk for various maternal and perinatal complications, which increase with the severity of obesity [356–358]. One-quarter of pregnancy complications are attributable to overweight or obesity [358]. Women with obesity and high gestational weight gain have the highest risks of pregnancy complications, and the latter is a potentially modifiable risk factor [359, 360].

Maternal overweight and obesity are associated with increased risks of adverse pregnancy outcomes both during and outside of pregnancy. Maternal complications include hypertensive disorders of pregnancy [361], gestational diabetes [247, 255, 362], and maternal mortality [9, 49]. Fetal or neonatal complications, including stillbirth [363], birth defects [49, 82], macrosomia [247, 364], and shoulder dystocia [365, 366], also occur more frequently in babies born to women with obesity, but reports are more variable for other possible adverse outcomes such as preterm delivery and early neonatal death [255].

The relative importance of obesity *per se* and hyperglycaemia to adverse pregnancy outcomes is difficult to ascertain from many previous studies due to methodological weaknesses. For example, in some reports routine screening for hyperglycaemia was not undertaken or not described [255]. In some studies that involved universal glucose screening, detailed analyses of the prevalence of GDM in women with overweight or obesity were not reported [367]. Moreover, in none of the previous studies were glucose results blinded from women or their caregivers, which may have influenced both clinical decision-making and ascertainment of pregnancy outcomes.

Excessive maternal weight gain is also associated with these same pregnancy and neonatal morbidities [359, 368] and, although GDM is associated with greater weight gain particularly in early pregnancy [369, 370], it is the weight gain that has the dominant effect on fetal growth [364]. Although GDM is associated with maternal obesity, the latter has a greater impact on these adverse outcomes [359, 364, 368]. Interpregnancy weight gain is also associated with poorer outcomes in subsequent pregnancies [371, 372].

Obesity in pregnancy increases the risk of GDM by a factor of 3.0 for women with moderate obesity and by 5.6 for women with morbid obesity [356]. The prevalence of GDM increases by 0.92% for each 1 kg/m^2 increase in BMI [356]. Insulin resistance is a hallmark of both obesity and GDM. All pregnant women have a reduced amount and phosphorylation of skeletal muscle insulin receptor (IRS1), the most important and abundant insulin receptor substrate in skeletal muscle, indicating a lower capacity for insulin signalling in pregnancy [373]. In women with pre-existing insulin resistance, the physiological rise in insulin resistance of pregnancy cannot always be compensated for by increased insulin secretion predisposing some women with obesity to develop GDM.

Interpretation of the relative clinical and population health importance of GDM and obesity, which frequently coexist, is difficult, as with few exceptions many studies fail to control for population heterogeneity, screening, and treatment [238, 239]. These problems were addressed by the large observational multicultural, multicentre HAPO study involving 23 000 untreated women during pregnancy with detailed characterization of GDM and weight status. In this study, obesity was present in 13.7% and GDM by IADPSG criteria in 16.1%; only 25% of the women with GDM had obesity [239, 240]. The HAPO study showed that maternal BMI and glycaemia have similar independent and essentially additive associations with adverse pregnancy outcomes [239, 240] (Figures 71.3 and 71.4). Maternal BMI was also strongly related to fetal adiposity and hyperinsulinaemia, even after adjustment for maternal glycaemia [239]. This highlights the potential importance of other nutrients including triglycerides, free fatty acids, and amino acids [374], and potentially total caloric intake. In addition, adipocytokines, inflammatory markers, and changes in physical activity may play a role in determining fetal size and adiposity [375]. Both maternal BMI and glucose were associated with increased frequency of caesarean section [255, 376]. The relative *importance* of these factors is heavily influenced by the potential costs and benefits of preventive or treatment strategies, which have practical and health-economic implications [377]. The same effects of gestational weight gain, independent of HbA_{1c}, are also observed in pregnancies of women with type 1 diabetes and type 2 diabetes [378, 379].

The US Institute of Medicine guidelines [213] (Table 71.6) suggest a total weight gain target of 5–9 kg for women with obesity during pregnancy, but even lower targets (including weight loss) might be associated with better outcomes [380, 381]. Compared with women with obesity who gain >5 kg during pregnancy, those who lose or gain <5 kg in weight in pregnancy have babies that are on average 190 g lighter (with a rate of SGA babies similar to women with normal weight) [382].

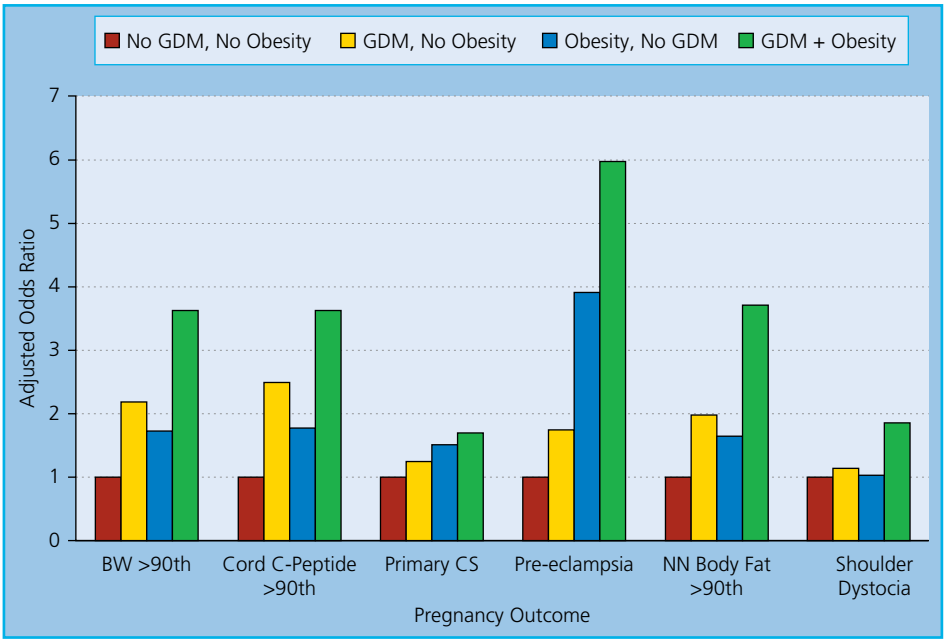


Figure 71.3 Odds ratios for pregnancy complications by obesity and gestational diabetes mellitus (GDM) status. Fully adjusted odds ratios for selected pregnancy complications in the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study. The 'No GDM, No Obesity' category served as the referent group for all complications. The other categories, as labelled, refer to GDM alone, Obesity alone, and the combination of both factors. Odds ratios refer to Model II as detailed in the original publication with full adjustment for potential confounders. BW, body weight; CS, caesarean section; NN, neonatal. Source: Data from Catalano et al. 2012 [240].

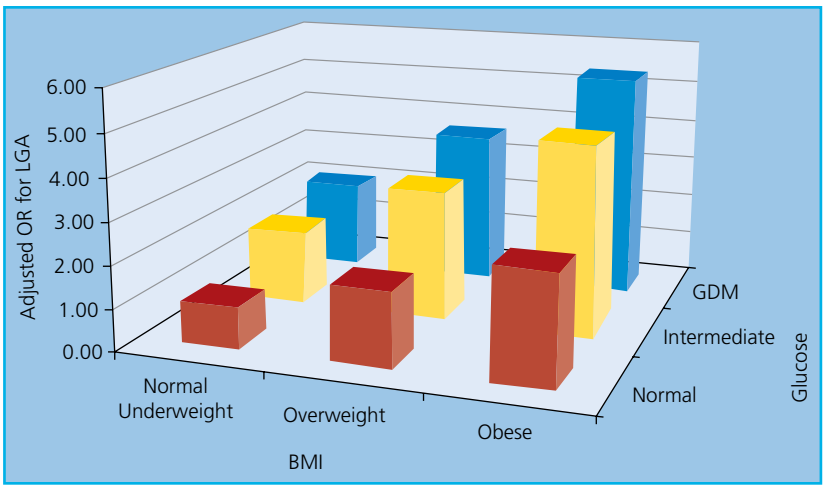


Figure 71.4 Odds ratios (OR) for a low-for-gestational age (LGA) infant divided by three category classifications of glycaemia and body mass index (BMI). Fully adjusted OR for delivery of an LGA infant characterized as birth weight >90th centile in Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study participants [240]. The group with normal glucose levels and normal- or underweight-range BMI served as the referent group. The intermediate glucose group was defined according to their mean standard deviation (Z) scores for the fasting, one-hour, and two-hour glucose levels during the diagnostic oral glucose tolerance test (OGTT). The values used to define this category were chosen to achieve a frequency of intermediate glucose equivalent to the frequency of overweight in the HAPO study cohort [238]. BMI was measured at the time of the diagnostic OGTT and converted to equivalent World Health Organization categories by regression analysis. GDM, gestational diabetes mellitus. Source: Data from Catalano et al. 2012 [240].

Malformations

Obesity is associated with an increased risk of congenital anomalies, including neural tube defects, cardiac malformations, orofacial defects, and limb-reduction abnormalities [82, 83]. The risk of most congenital abnormalities, including neural tube defects and congenital heart defects, increases with the severity of maternal obesity [82, 83], with the exception of gastroschisis. An analysis of the Florida Birth Defects Registry showed an increase in prevalence of birth defects in live-born infants, increasing from 3.9% in underweight women to 5.3% in those with obesity with BMI >40 kg/m^2 [383]. Maternal obesity reduces the chances of detecting congenital anomalies antenatally by 23% [384]. The mechanism for these associations is not well defined, but is likely related to an altered nutritional milieu during fetal development.

Effects on neonatal complications

Offspring of women with obesity have greater Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), leptin, and interleukin-6 measurements in cord blood [385], a marginal increase in birth weight, no change in lean body mass, but a significant increase in percentage body fat from 9.7% to 11.6% [386]. The risk of LGA infants increases with greater maternal weight gain in obesity [368]. Compared with normal-weight euglycaemic women, the odds for LGA, adjusted for weight gain during pregnancy, were 1.96 for normal-weight women with GDM, 2.63 for women with obesity but not GDM, and 5.47 for women with both obesity and GDM [387]. Infants born to women with obesity and morbid obesity are at increased risk of neonatal hypoglycaemia, premature delivery, admission to intensive care, and jaundice. The effects of maternal diabetes and maternal obesity on the offspring are both additive and independent.

Long-term outcomes for the mother

In women with a history of GDM, the risk of recurrent GDM is 30–84% [342]. GDM is a risk factor for type 2 diabetes and indeed the original diagnostic thresholds were defined on this basis [239]. Even a slight elevation in blood glucose during a screening oral glucose challenge test or a diagnostic OGTT, or isolated

hyperglycaemia at one hour during an OGTT, is associated with an increased risk of postpartum hyperglycaemia [388].

A meta-analysis of 20 studies in 2009 demonstrated that women with previous GDM had a 4.7-fold risk of developing diabetes within five years of having GDM, 9.3-fold after five years or more, compared with a normoglycaemic pregnancy [389]. An estimated 17–50% of women with prior GDM will develop type 2 diabetes within 1–5 years of pregnancy; this increases to 35–70% at 10–20 years after the index pregnancy [388–392]. The lifetime risk of type 2 diabetes is up to 10 times higher [343, 344]. The absolute risk increases linearly through a woman's lifetime, being approximately 20% at 10 years, 30% at 20 years, 40% at 30 years, 50% at 40 years, and 60% at 50 years [344].

Postpartum diabetes is a multifactorial condition involving the interaction of modifiable and non-modifiable risk factors. Previous studies have identified various risk factors, including maternal age, family history of diabetes, glycaemic indices during pregnancy, weight, healthy diet, exercise, and breastfeeding [393, 394]. Those women with the highest blood glucose levels at diagnosis of GDM, those who needed insulin treatment in pregnancy, those with impaired β-cell function, and those who are overweight and gain most weight after their GDM pregnancy tend to develop type 2 diabetes the earliest [395, 396].

A problem with follow-up studies has been the variable definitions of GDM and lack of control for confounding variables. Of particular importance in this regard is the Hyperglycaemia and Adverse Pregnancy Outcomes Follow-Up Study (HAPOFUS) [254, 397–401], involving 4679 mothers (mean age 41.7 years). At a median of 11.4 years of follow-up, 52.2% of mothers with untreated GDM during pregnancy developed a disorder of glucose metabolism versus 20.1% of mothers without GDM (OR 3.44; 95% CI 2.85 to 4.14). More than twice as many mothers with IADPSG-defined GDM compared with mothers with Carpenter–Coustan criteria-defined GDM (240 vs 106) developed a disorder of glucose metabolism [254].

The similarities in risk factors for the development of GDM and type 2 diabetes have long been recognized. Women studied at the time of normal glucose tolerance present with the hallmarks of insulin resistance and hyperinsulinaemia [402]. Indeed, GDM is best regarded as a form of type 2 diabetes, with the same risk factors [401]. Other studies [403, 404] highlight the greater prevalence of a cluster of cardiovascular factors such as obesity (BMI ≥30 kg/m^2), hypertension, and dyslipidaemia in women with previous GDM, with the prevalence of the metabolic syndrome being 40% (three times that of the control group) [405].

In several large-cohort observational studies [319, 405], higher rates of incident ischaemic heart disease were observed independent of the onset of type 2 diabetes. Women with prior GDM have 1.95-fold higher odds of developing cardiovascular disease compared to women without GDM [406]. The lifetime risk of cardiovascular disease following GDM was most marked in those women who progressed to overt type 2 diabetes (hazard ratio [HR] 2.82; 95% CI 2.24 to 3.30), but an increased risk (HR 1.41; 95% CI 1.11 to 1.80) was present even for women without progression. In addition, a recent Canadian population-based study [317] showed that women with hyperglycaemia who did not meet the diagnostic thresholds for GDM still had a higher risk of cardiovascular disease, although some of these women might have met the more stringent IDAPSG/WHO criteria.

These data highlight that GDM and hyperglycaemia in pregnancy are associated with a high risk of both diabetes and future cardiovascular disease. The management strategy should involve the comprehensive identification and systematic treatment of risk factors for both conditions.

Long-term outcomes for the offspring

Infants of mothers with hyperglycaemia in pregnancy (both pre-existing and gestational) are more likely than infants of normoglycaemic mothers to be born LGA as a consequence of excess fetal growth and adiposity. The HAPO study showed a linear independent association between maternal glycaemia and odds of LGA birth weight, with an odds of 1.38 for each standard deviation increase in maternal fasting glucose [238]. Hyperglycaemia is independent of maternal obesity and excessive gestational weight gain, which also contribute to this risk [239]. Excess adiposity in the offspring can be independent of birth weight [407].

Infants of women with diabetes are at increased risk of certain chronic diseases, including obesity, diabetes, and the metabolic syndrome in later life, with implications for public health [254, 397–401, 406, 407]. In addition, the Pedersen hypothesis has been expanded to envisage a role for other fuels besides glucose *fuel-mediated teratogenesis*, later encapsulated in the developmental origins hypothesis, in which hyperglycaemia *in utero* is envisaged to drive the development of obesity and diabetes through fetal metabolic programming [408]. Under this hypothesis, such conditioning in female offspring could increase the propensity to GDM and hence lead to a transgenerational cycle with major public health implications [409].

Similar concerns pertain to the global increase in childhood obesity [410–413], where current prevalence rates indicate that by the age of 2 years, one in ten children in the USA have obesity and more than half will have obesity by the age of 35 years [413]. This persistence of obesity into early adulthood is likely to increase the risk of type 2 diabetes and cardiovascular disease.

A problem in the interpretation of long-term outcome studies is that some of the earlier studies were conducted in populations with a high prevalence of diabetes, many fail to control for confounding variables, and alternative explanations for the associations, such as shared genetic or familial associations, are possible. The original seminal long-term studies in the Pima, a population with a very high prevalence of type 2 diabetes, showed that offspring of women with type 2 diabetes during pregnancy had an increased risk of early-onset type 2 diabetes compared with offspring of mothers without diabetes [414]. Similar findings were reported from an ethnically diverse population from Chicago (with a lower background prevalence of type 2 diabetes), in which the prevalence of impaired glucose tolerance among offspring exposed to maternal pregestational GDM *in utero* was 20% by the age of 16 years (10 times higher than in the general population of similar age) [415]. The prevalence of type 2 diabetes or pre-diabetes among adult offspring of Danish women with GDM was 21% compared to 12% among offspring of women screened for GDM but found to be negative [416]. Elevated rates in the prevalence of type 2 diabetes or pre-diabetes were also reported in the offspring of women with type 1 diabetes [416, 417]; the prevalence of type 2 diabetes or pre-diabetes was 11% in Danish adult offspring of women with type 1 diabetes compared with 4% in offspring of women without diabetes. In support of the intrauterine environment over shared genetic and environmental factors, studies in the Pima showed that siblings born before the mother's diagnosis of type 2 diabetes had a lower prevalence of diabetes and a lower mean BMI compared to their sibling born after the diagnosis [418]. Other studies have observed an excess frequency

of maternal versus paternal transmission of diabetes [419], although this finding has not been consistent across all studies [420].

In the Pima, offspring of mothers with type 2 diabetes during pregnancy were at greater risk of obesity and higher body weight for age than offspring of women with pre-diabetes or without diabetes [421], but obesity in the offspring was significantly related to both maternal and paternal BMI [422]. These findings have been confirmed in other population groups [423]. Similarly, offspring of mothers with GDM have an increased risk of developing the metabolic syndrome [345] and have other cardiovascular risk [346] independent of birth weight [345]. These risk factors have also been found in offspring of women with type 1 diabetes [424].

The higher prevalence of obesity among women with GDM confounds the association of GDM with childhood obesity. Higher maternal BMI is associated with higher childhood adiposity through shared genetics, familial lifestyle and environmental factors, and the intrauterine environment [425]. Both maternal and paternal BMI are positively associated with obesity and high waist circumference in the offspring [426, 427], which could be interpreted on the basis of shared genetic factors and a shared postnatal environment [428]. Adjustment for parental obesity and for postnatal environmental factors may be important to avoid confounding bias in studies of the long-term risk of obesity associated with intrauterine exposure to diabetes [428–430]. Adjustment for maternal BMI has resulted in inconsistent results and in some studies attenuated the associations between GDM and childhood obesity, leading to the question of whether the association was independent [431, 432].

Mechanistically, it is possible that adjustment for maternal prepregnancy BMI may partially obscure the full effect of fetal overnutrition due to its contribution to a fuel-rich environment and elevated intrauterine glucose [433]. In addition, maternal screening for GDM is often not universal and is more likely to be offered to women with overweight or obesity, resulting in underdiagnosis of GDM among normal-weight women and consequently underestimation of the true association between maternal and offspring obesity/diabetes after adjustment for maternal BMI. On the other hand, animal models have demonstrated altered epigenetic regulation leading to altered cellular signalling [434], or disturbances in the development of central fetal pathways controlling appetite and energy balance [435].

Against this background, the HAPO follow-up study of 4832 children at a median duration of follow-up of 11.4 years reported that 39.5% of the offspring of women with GDM had overweight or obesity and 19.1% had obesity, compared with 28.6% and 9.9%, respectively, in offspring of normoglycaemic mothers [254, 397]. The study showed that IADPSG-defined GDM, independently of maternal BMI, was associated with childhood obesity as well as direct measures of child adiposity, such as sum of skin folds or body fat percentage. These associations were stronger than the associations with BMI, likely reflecting contributions of both fat and lean body mass to BMI. This was consistent with the independent and additive effects of maternal and GDM on newborn adiposity outcomes in the HAPO study [238, 239].

Whether an association of GDM with newborn and childhood outcomes is mediated solely through mixed nutrients (e.g. sugars, lipids, and amino acids), as proposed by Freinkel [436], remains to be determined. However, recent metabolomic studies performed within the HAPO study and within other cohorts support the concept that mixed nutrients contribute to associations of maternal hyperglycaemia with newborn outcomes [437].

Lifestyle intervention trials during pregnancy

Recent lifestyle interventions during pregnancy are detailed in Table 71.15 [438–447, 450–452]. Lifestyle interventions in pregnant women with obesity may have the potential to limit gestational weight gain, which is important for reducing postpartum weight retention and limiting pregestational weight in a subsequent pregnancy. Lifestyle interventions are generally difficult to undertake and often labour intensive [453]. They frequently differ in the combination of behavioural, dietary, and physical activities, and the intensity and monitoring of fidelity, thus making comparisons difficult. Other limitations include the likelihood of attracting the healthiest women, lack of blinding, and commencement of interventions too late in pregnancy. The Finnish Gestational Diabetes Prevention Study (RADIEL) [446], involving women at high risk of GDM and ~30% with previous GDM, showed a reduction in GDM, but other studies have not shown any reduction in clinical, maternal, and neonatal outcomes such as GDM, pre-eclampsia, macrosomia, and preterm birth. Pregestational BMI is a stronger predictor of maternal and neonatal pregnancy outcomes than gestational weight gain [364] and these women have more insulin resistance and higher circulating plasma triglycerides from the beginning of pregnancy [454]. Several studies have shown the importance of interpregnancy weight change for the risk of complications in the next pregnancy [371, 372]. A mild to moderate interpregnancy weight loss in women with obesity significantly reduces the risk of subsequent LGA infants in observational studies without increasing the risk of SGA infants.

A 2015 Cochrane review of 13 RCTs and 4983 women and their babies assessed the effects of combined diet and exercise interventions and reported that diet and exercise interventions did not change the risk of developing GDM [455]. This was also found in other systematic reviews and meta-analyses [456–459]. Several reviews indicated that some antenatal interventions are associated with reduced gestational weight gain, and it seems that dietary interventions are most effective; however, studies need to be interpreted cautiously given that they are generally of low/moderate quality.

Telehealth interventions are growing in popularity for use in pregnancy for conditions such as GDM [460], although trials to date have been undertaken in highly select groups of individuals. Other concerns include usability of technology, reliability of data, and ability to inform clinical decision making, but with continuing development and refinement of technologies they seem to offer promise.

No intervention studies have been shown to reduce the long-term impact of GDM during pregnancy on both mother and baby. Taken together, the findings highlight the importance of optimizing maternal pregestational body weight and the metabolic conditions before conception. The interpregnancy interval may be a crucial period for targeting weight loss in future studies. In the meantime, gestational weight gain should be avoided, healthy eating and an active lifestyle promoted, and breastfeeding and weight loss supported after pregnancy.

Postnatal intervention trials

Given the increased risk of type 2 diabetes after pregnancy in women with GDM, and the importance of prepregnancy BMI and interpregnancy weight gain, intervention trials have also investigated modifiable risk factors [393, 394] after pregnancy, with the aim of improving the postpartum metabolic phenotype and reducing the incidence of type 2 diabetes.

Table 71.15 Lifestyle intervention trials during pregnancy.

Author (year) Study [reference]	Design	Population	Intervention	Results
Phelan (2011) Fit for Delivery [438]	RCT, intervention vs control	BMI 19.8–40 kg/m^2; USA; n = 401	Low-intensity behavioural intervention; one F2F contact with interventionist at study entry and 3 short supportive phone calls	Reduction in exceeding 1990 IOM criteria for GWG: 40.2% vs 52.1%; p = 0.003 (normal weight only); no significant effect on GWG in overweight/obese
Luoto (2011) NELLI [439]	Cluster RCT, intervention vs control	All BMI groups; euglycaemic but at least one GDM risk factor; Finland; n = 399	5 F2F antenatal visits with nurses, with individual dietary and exercise counselling	No effect on GWG (13.8 vs 14.2 kg; p = 0.52); significantly lower birth weight in intervention group vs control: 3532 vs 3659 g (p = 0.008); and significant reduction in birth weight/week and LGA; no effect on GDM or macrosomia
Vinter (2011) LIP [440]	RCT, intervention vs control	BMI ≥30 kg/m^2; Denmark; n = 360	4 individual F2F visits with dietitians, weekly training sessions in groups with physiotherapists, pedometer and free fitness club membership	Significant reduction in GWG: 7.0 vs 8.6 kg; p = 0.01; no effect on birth weight, LGA, or GDM
Walsh (2012) ROLO [441]	RCT, intervention vs control	2nd pregnancy; prior infant >4000 g; Ireland; n = 800	Low glycaemic index diet from early pregnancy (1 group session with dietitians); follow-up with written material and 2 sessions with reinforcement	No significant difference in birth weight or macrosomia; significant reduction in GWG: –1.3 kg (95% CI –2.4 to –0.2); p = 0.01
Bogaerts (2013) [442]	RCT, 3 groups: lifestyle, brochure, and control	BMI ≥29 kg/m^2; Belgium; n = 205	Brochure group received written information on healthy lifestyle; lifestyle group had 4 antenatal intervention sessions with midwives trained in motivational interviewing	Significant reduction in GWG in both intervention groups vs control: 9.5 vs 10.6 vs 13.5 kg; p = 0.007; significantly less anxiety in active lifestyle group only; no effect on birthweight or GDM
Renault (2014) TOP [443]	RCT, 3 groups: physical activity (PA) + Diet, PA, and control	BMI ≥30 kg/m^2; Denmark; n = 425	Dietary advice by dietitians every 2 weeks (F2F and phone calls); PA included pedometer with encouragement to aim for 11 000 steps daily	Significant reduction in GWG in both intervention groups vs controls: 8.6 vs 9.4 vs 10.9 kg; p = 0.01; no effect on birth weight, LGA, or GDM
Dodd (2014) LIMIT [444]	RCT, intervention vs control	BMI ≥25 kg/m^2; Australia; n = 2212	Dietary, exercise, and behavioural strategies delivered by dietitians and assistants at 2 F2F visits followed up by 3 personal phone calls	No reduction in LGA in intervention vs control: 19% vs 21%; p = 0.24; significantly lower rate of macrosomic infants (>4000 g): 15% vs 19%; p = 0.04; no difference in GWG: 9.39 vs 9.44 kg; p = 0.89
Poston (2015) UPBEAT [445]	RCT, intervention vs control	BMI ≥30 kg/m^2; UK; n = 1555	Behavioural intervention; 8 weekly health trainer-led sessions in groups or individualized	No difference in GDM between intervention vs controls: 25% vs 26%; p = 0.68; no difference in LGA: 9% vs 8%; p = 0.40; significant reduction in GWG: 7.19 kg vs 7.76 kg; p = 0.041
Koivusalo (2015) RADIEL [446]	RCT, intervention vs control	BMI ≥30 kg/m^2; Finland; n = 293	Individual counselling on diet, physical activity, and weight control from study nurses and one group meeting with dietitian	GDM incidence 13.9% (intervention) vs 21.6% control (95% CI 0.40 to 0.98%; p = 0.044) after adjustment for baseline variables; significant reduction in GWG: –0.58 kg (95% CI –1.12 to –0.04); adjusted p = 0.037
Simmons (2017) DALI [447]	RCT, 3 groups: healthy eating (HE), physical activity (PA), and HE + PA	BMI ≥29 kg/m^2; 9 European countries; n = 436	5 F2F and 4 optional telephone coaching sessions; based on principles of motivational interviewing	Significantly lower GWG in HE women: –2.02 kg; 95% CI –3.58 to –0.46. No difference in fasting glucose/insulin resistance; no significant difference between HE + PA and other groups; GDM prevalence similar in all intervention groups
Dodd (2019) GROW [450]	RCT, (dietary + lifestyle) + metformin vs placebo	BMI ≥25 kg/m^2; 10–20 weeks' gestation; Australia; n = 514	Dietary and lifestyle intervention with additional metformin or placebo	No significant difference in birth weight >4000 g (16% metformin vs 14% placebo); metformin group had significantly lower average weekly GWG (–0.08 kg; 95% CI –0.14 to –0.02; p = 0.007). No difference in total GWG or pregnancy and birth outcomes
Ferrara (2020) GLOW [451]	RCT, telehealth lifestyle intervention vs usual antenatal care	BMI 25–40 kg/m^2; 8–20 weeks' gestation; USA; n = 398	2 F2F and 11 telephone sessions on behavioural interventions	48% women in lifestyle vs 69% in control exceeded IOM recommendations for GWG/week (relative risk 0.70, 95% CI 0.59 to 0.83); mean between-group difference lifestyle vs control: (–0·07 kg/wk, 95% CI –0·09 to –0·04). No between-group differences in perinatal complications
Yew (2021) SMART-GDM [452]	RCT, smartphone-based lifestyle-based coaching programme vs usual care	GDM; 12–30 weeks' gestation; mean BMI 25.6 kg/m^2; Singapore; n = 340	Smartphone-based lifestyle-based coaching program vs usual care	With intervention, no significant reduction in excessive GWG (primary outcome), absolute GWG, or maternal or delivery outcomes; significant reduction in average glucose readings and composite outcome (not prespecified) of neonatal complications (38.1% vs 53.7%)

BMI, body mass index; CI, confidence interval; F2F, face-to-face; GDM, gestational diabetes mellitus; GWG, gestational weight gain; IOM, Institute of Medicine; LGA, large for gestational age; RCT, randomized controlled trial.

Pharmacological interventions

A significant dose-dependent increase in insulin sensitivity and a reduced insulin response were observed in women with previous GDM who had been randomized to either 200 or 400 mg/d troglitazone [461], with participants in the TRoglitazone In the Prevention Of Diabetes (TRIPOD) trial randomized to the troglitazone (400 mg/d) group demonstrating a 55% reduction in the risk of diabetes progression [462]. The US Diabetes Prevention Program (DPP) demonstrated that metformin reduced the cumulative incidence of diabetes in women with impaired glucose tolerance and previous GDM by 50.4% compared with placebo [463, 464]. The results of this study suggest that interventions such as metformin treatment are effective for preventing the progression to diabetes, even many years after delivery.

Breastfeeding

Lactation improves glucose tolerance in the early postpartum period, but it remains uncertain whether future risk of type 2 diabetes is reduced, with only a few studies having examined breastfeeding and postpartum glucose tolerance in women with previous GDM. Ziegler et al. followed women with GDM for up to 19 years and found that breastfeeding for >3 months reduced postpartum diabetes by 46% [465]. A 12-year follow-up in the Nurses' Health Study reported that increasing duration of lactation was associated with reduced risk of type 2 diabetes, with each additional year decreasing the risk by 15% [466]. However, when stratified by GDM status, no association between lactation and risk of type 2 diabetes was evident.

Physical activity

Physical activity reduces the incidence of type 2 diabetes in both the general population and in those with a history of GDM. A large 16-year prospective cohort study showed that increasing physical activity may help lower the risk of progression from GDM to type 2 diabetes [467]. A small feasibility study assessing a structured behavioural intervention to increase physical activity in women failed to achieve its goal of increasing step count to 10 000 steps/d [468]. Interventions involving the promotion of physical activity alone are limited, with the majority of trials utilizing a multicomponent lifestyle approach of which physical activity is one behaviour.

Diet

Following a healthy dietary pattern reduces the risk of developing diabetes [469]. In women with obesity and previous GDM, a weight loss regimen consisting of 40% versus 55% carbohydrate resulted in similar weight loss, although the former had lower triglyceride levels [470]. Asian women who followed a low glycaemic index eating plan reported significant reductions in body weight, BMI, and waist-to-hip ratio at six months postpartum [471]. Among participants in the Nurses' Health Study II cohort with a history of GDM, those consuming diets within the highest quartile for the Mediterranean diet, Dietary Approaches to Stop Hypertension (DASH) diet, and alternate Healthy Eating Index diet had a 40–57% lower risk of developing postpartum diabetes compared with women in the lowest quartile over a 14-year follow-up period [472]. Studies implementing dietary change during pregnancy in women with GDM have reported positive results for the duration of the index pregnancy; however, changes were not sustained postpartum [473, 474], highlighting the need to identify strategies to encourage continued engagement during the postpartum period. Loss of 10–15% of body weight through dietary modification can result in remission of type 2 diabetes [475, 476].

Diet and physical activity

Combined diet and physical activity promotion programmes aim to prevent type 2 diabetes [477], with weight loss being the risk factor explaining the greatest variance in risk and the one most amenable to change [478]. While outcomes such as weight loss and reduction in BMI have been successfully achieved in combined interventions [479, 480], this has not consistently translated into a reduced incidence of the development of type 2 diabetes [481, 482]. Ratner et al. found lifestyle modification to be as effective as treatment with metformin in reducing the incidence of diabetes by 50% compared with controls [464]. A more recent Spanish study reported that after three years' follow-up fewer women assigned to a diet and physical activity intervention group developed glucose disorders than the control group [483]. Further studies are needed to elucidate which are the key features to optimize the effectiveness of these programmes by translating them into long-term health outcomes.

Lifestyle interventions with a telephone component

Numerous studies have examined the effect of lifestyle interventions delivered either in full or partially via telephone in women with a history of GDM. A US phone intervention based on DPP guidelines (diet, exercise, breastfeeding) versus controls observed no difference in the proportion of women achieving their prepregnancy weight at 12 months postpartum [484]. Two Australian studies comprising phone-based behavioural interventions reported no effect on weight, BMI, or physical activity [485, 486]. A large US study of 2280 women with GDM observed that women receiving 13 DPP-based phone sessions over a 12-month period had higher odds of meeting weight goals at 6 weeks, 6 months, and 12 months postpartum and of achieving greater increases in vigorous-intensity physical activity [487]. Two years following delivery of a lifestyle intervention underpinned by motivational interviewing techniques, Hedderson et al. observed a decrease in total energy intake and percentage of calories from fats, and increase in physical activity in women who received the intervention compared with controls [488]. Many of these trials use multiple methods of delivery, making it difficult to ascertain which precise elements are exerting the greatest effect. The delivery of an intervention remotely by telephone is attractive, as it often reduces the need for the woman to leave the home or arrange childcare when attending appointments. The effectiveness of remote/partially remote programmes needs to be further investigated.

Lifestyle interventions with a digital component

The proliferation of mobile devices has facilitated the design, development, and delivery of remote digital interventions, which have the potential to introduce lifestyle change by supplementing or replacing face-to-face contact. Web-based education, pedometers, text message reminders, internet forums, emails, and apps have all been utilized in RCTs for women with previous GDM in recent years. Some studies have demonstrated significant improvement in post-intervention weight loss [489, 490], but others have shown no effect [485, 491]. Glycaemic indices remained similar between intervention and control groups [492, 493]. The possibility of utilizing digital technology to assist with the delivery of health promotion interventions is attractive for both the service provider and the service user [494]. However, the pace of development of technology necessitates regular monitoring and updating of devices and systems to remain relevant. The identification of key intervention components needs to be prioritized in future studies. Lack of standardized reporting and timepoint of assessment presents a barrier to

direct comparison between trials. Research is needed into the development of a core outcome set with which to facilitate direct comparison or combination of results from different studies.

Probiotics

Given the role of gut microbiota in regulating metabolism, there has been interest in the possible role of probiotics in prevention of GDM. A Finish study involving 256 pregnant at-risk women, who were randomized in the first trimester to probiotic dietary intervention or control, showed a reduction in maternal glycaemia and rate of GDM in the intervention group (36 vs 13%) [495], but these results were not replicated in two more recent studies in women with obesity at high risk of GDM [496, 497].

Future work

Current evidence would suggest a benefit of diet and exercise in women at risk of GDM [498, 499], but the results of interventions during pregnancy have generally been disappointing and studies are of variable quality. Future trials may need to be started much earlier in pregnancy and particularly focused on women between pregnancies and those women planning pregnancy.

Most cases of type 2 diabetes can be prevented or significantly delayed by lifestyle intervention and the use of metformin. Only five to six women with a history of GDM and pre-diabetes need to be treated with either intervention to prevent one case of diabetes over three years [464]. Recent data have highlighted the importance of weight loss both to reduce risk and to effect remission of type 2 diabetes. These lines of evidence would suggest that women with GDM and their families form a key high-risk group for whom there is a compelling case for targeted intervention. Intervention trials in women with previous GDM, investigating modifiable risk factors to improve the postpartum metabolic phenotype and reduce future incidences of type 2 diabetes, have demonstrated considerable promise; however, these women face various obstacles to implementing lifestyle changes, and as a result attrition of women with GDM to follow-up evaluations after delivery is problematic. The main factors include time pressure, emotional stress in adjusting to a baby, and poor social support [448, 449]. Successful translation of pragmatic lifestyle interventions into effective evidence-based practice needs to address and overcome these challenges. Further long-term offspring studies are needed, but to date the efficacy of GDM treatment during pregnancy in preventing long-term offspring complications remains unproven, with negative results reported both by the ACHOIS study [320] and the MFMU trials [321].

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72 Diabetes in Old Age

Ahmed H. Abdelhafiz[1] and Alan J. Sinclair[2]

[1] Department of Elderly Medicine, Rotherham General Hospital, Rotherham, UK

[2] Foundation for Diabetes Research in Older People (fDROP) and King's College London, London, UK

Key points

- The prevalence of diabetes is increasing in older people because of increased life expectancy.
- The phenotype of diabetes in old age is characterized by an increased prevalence of multiple comorbidities, geriatric syndromes, and frailty.
- A comprehensive geriatric assessment should be performed at the initial diagnosis of diabetes and annually thereafter.
- A multidisciplinary team approach with a multidimensional assessment, including screening for physical and cognitive function, is important to meet the complex needs of older people with diabetes.
- Hypoglycaemia is common in older people with diabetes owing to multiple comorbidities, and can be less easily recognized or misdiagnosed because of reduced autonomic symptoms.
- Increasing glucose levels, unexplained hypoglycaemia, or reduced self-care should alert the clinician to the presence of dementia or depression.
- Tight glycaemic targets are reasonable in fit older people, but a relaxed approach is more appropriate in frail older people at risk of hypoglycaemia.
- An individualized and holistic care plan is key to diabetes care in older people.
- Older people with diabetes living in care homes are particularly vulnerable and require greater specialist input.
- Quality of life should always be the focus for individualized care.

With the increasing ageing of the population, changing lifestyle and urbanization, the prevalence of diabetes has or is likely to reach epidemic levels in most countries, especially in older people ≥75 years [1]. Ageing is associated with body composition changes that lead to increased insulin resistance, glucose intolerance, and increased risk of diabetes [2]. As a result, more older people are developing diabetes. The lifetime risk of developing diabetes is high, reaching 22.4% for women and 18.9% for men from the age of 60 years [3]. Older people with diabetes are exposed to the interplay between metabolic dysfunction, vascular disease, and the ageing process in combination with other age-related disorders. Geriatric syndromes and frailty are emerging as a third category of complications in addition to the traditional micro- and macrovascular disease [4]. Therefore, diabetes in old age may lead to considerable disability. Unlike other chronic conditions, diabetes care is dependent on self-management, which may be compromised by the presence of comorbidities and geriatric syndromes. Owing to the heterogeneous nature and variations in comorbidity, life expectancy, and functional status, ranging from a fit individual living independently in the community to a fully dependent person living in a care home, therapeutic interventions and metabolic targets should be individualized, taking into consideration individual preference while putting quality of life at the heart of the care plan. This chapter reviews the phenotype of diabetes in old age and addresses the key areas and special considerations for the care of older people with diabetes to meet their complex needs.

Epidemiology

In 2017, about 8.4% of the world population had diabetes and this is expected to reach 10% in 2045 [1]. The prevalence of diabetes rises with increasing age. Worldwide, the greatest proportional increase in the number of people with diabetes by age group is expected to occur in those aged 60–79 years [3]. For example, in France, the prevalence has increased to 14.2% in people aged 65–74 years, peaking at 19.7% in men and 14.2% in women aged 75–79 years. More than half of those with diabetes were ≥65 years [5]. In the USA, 14% of the population is estimated to have diabetes and the prevalence is highest in those aged ≥65 years; by 2050 diabetes prevalence could be as high as 33% of the whole population [6]. Furthermore, a similar number may remain undiagnosed. In the US National Health and Nutrition Examination Survey, the prevalence of diagnosed diabetes in those ≥75 years was 14.9% and undiagnosed diabetes based on fasting plasma glucose and two-hour oral glucose tolerance test was 13.4%, making a total prevalence of diabetes of 28.3%, with undiagnosed diabetes constituting ~47%. The prevalence of *pre-diabetes*, defined as either impaired fasting glycaemia or impaired glucose tolerance, was 46.7% in those aged ≥75 years. Therefore, the total prevalence of diabetes and pre-diabetes was ~75% in older people ≥75 years [1].

Low- and middle-income countries will have the greatest burden of diabetes, where the prevalence will increase in adults

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(aged 20–79 years) by 69% by 2030 compared to only 20% in higher-income countries [7]. This is likely driven by the growth and ageing of the population, changing lifestyle and urbanization in these countries. The prevalence of diabetes among older Chinese in rural Taiwan aged 72.6 years was 16.9% in 2000 and increased to 23.7% in 2005 [8]. In minority ethnic groups living in high-income countries, the incidence and prevalence of diabetes are higher than in white European populations. For example, the prevalence of diabetes in older Mexican Americans (≥75 years) almost doubled between 1993–1994 and 2004–2005, from 20.3% to 37.2%, in comparison to an increase from 10.4% to 16.4% in the general population of the same age [9].

Diabetes prevalence in care homes is also high. In 2004, 24.6% of US nursing home residents had diabetes; among residents aged 65–74, 75–84, and ≥85 years, the prevalence of diabetes was 36.1%, 29.5%, and 18.3%, respectively [10]. The prevalence of diabetes steadily increased in US nursing homes (16.9% to 26.4% in men and 16.1% to 22.2% in women) between 1995 and 2004. A more recent survey showed a further increase in the prevalence of diabetes, with 32.8% of residents living with diabetes [11]. Ethnic disparities in diabetes prevalence are also well documented in care home settings. In US nursing homes, the adjusted odds of diabetes are approximately twofold higher in African American and Hispanic residents relative to white American residents, present in 22.5% of white Americans and 35.6% of those from other ethnic groups [10].

Pathogenesis

Glucose homeostasis requires both normal insulin secretion by the pancreatic β cells and normal glucose utilization by the peripheral tissues that are sensitive to insulin. Diabetes in old age is linked to increased insulin resistance and decreased insulin secretion, with a principal defect of insulin resistance in individuals with obesity and insulin secretion in those who are lean. It is likely that both genetic and environmental factors are involved in the pathogenesis of the insulin secretory dysfunction and insulin resistance. As older people are heterogeneous, the extent and rate of deterioration in glucose homeostasis are variable, leading to insignificant changes in some individuals and diabetes in others (Box 72.1).

Increased insulin resistance

Ageing is associated with body composition changes that result in increased insulin resistance [12]. Increased visceral fat is associated with increased rates of lipolysis causing high levels of free fatty acids, which may have a role in reducing peripheral insulin sensitivity [13]. Reduction of muscle mass or sarcopenia occurs with ageing through physical inactivity and, as the muscle is the main site of glucose consumption, the loss of muscle mass increases insulin resistance [12]. Accumulation of lipids within the muscles is another factor reducing insulin sensitivity. A reduction in mitochondrial function [14] may also contribute to age-related glucose intolerance by reducing oxidative metabolism, physical fitness, and oxidative capacity. Low concentrations of adiponectin, leptin, and insulin-like growth factor I (IGF-I), and high concentrations of tumour necrosis factor α (TNF-α), are associated with ageing and linked to increased insulin resistance and incident diabetes [14–16].

Decreased insulin secretion

Insulin secretion diminishes by 0.7% per year with increasing age because of reduced function and increased apoptosis of pancreatic β cells [17]. β-cell autoimmunity may lead to activation of an acute-phase response in older people with diabetes, with hypersecretion of interleukins, C-reactive protein, and TNF-α, which may reduce insulin secretion [18]. Disturbances in the physiology of the gut-derived incretins, gastric inhibitory polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), may be another factor involved in β-cell dysfunction [19]. Both peptides enhance insulin secretion after meals and may have a role in maintaining β-cell growth, proliferation, and inhibition of apoptosis. Ageing is associated with reduced levels and function of these peptides [20].

Box 72.1 Determinants of glucose intolerance in old age

- Decreased β-cell function.
- Reduced β-cell mass.
- Increased visceral fat.
- Reduced muscle mass.
- Mitochondrial dysfunction.
- Low concentrations of adiponectin.[a]
- High concentrations of tumour necrosis factor α.[b]
- Reduced insulin-like growth factor I concentration.[c]
- Reduced leptin concentration.[d]
- Physical inactivity.
- Altered lipid metabolism.

[a] Secreted by adipose tissue, improves insulin resistance by increasing fat oxidation.
[b] Induces anorexia, weight loss, and insulin resistance.
[c] A peptide hormone that stimulates glucose uptake.
[d] Secreted by adipose tissue, decreases appetite, and its decline may contribute to the increased adiposity and body composition changes seen in older people.

Diabetes phenotype in old age

Diabetes in older people is associated with coexistent multiple comorbidity burden, geriatric syndromes, and frailty (Box 72.2).

Comorbidity burden

Diabetes in older people is associated with increased atherosclerosis, premature ageing, and increased disability. Older people with

Box 72.2 Diabetes phenotype in older people with diabetes

- Multiple comorbidities.
- Cognitive dysfunction.
- Depression.
- Physical dysfunction.
- Falls and fractures.
- Urinary incontinence.
- Polypharmacy.
- Less muscle mass and poor muscle quality.
- Malnutrition.
- Frailty.
- Nutritional need and hydration.
- Irregular eating pattern, especially in people with dementia.
- Vulnerability to hypoglycaemia.

diabetes frequently have at least one comorbid chronic disease in addition to diabetes, and as many as 40% have at least three conditions [21]. The comorbidity burden is even higher in care home residents with diabetes. For example, those with diabetes have more cardiovascular disease, visual problems, pressure sores, limb amputations, and kidney failure than residents without diabetes [22]. In a retrospective case note review of 75 nursing home residents with diabetes in the UK, significant levels of disability were shown in areas of continence, feeding, mobility, and communication. The average number of comorbidities per individual was 4 (range 1 to 8) [23]. The mortality rate was 34% after one year of follow-up, indicating severe comorbidity [24]. In another study, residents with diabetes had a greater comorbidity burden (Hierarchical Condition Category 1.90 vs 1.58), were prescribed more medications, and experienced more hospitalizations (37% vs 18%) than residents without diabetes [11].

Geriatric syndromes

Geriatric syndromes, such as cognitive and physical dysfunction, depression, falls, and urinary incontinence, are common in older people with diabetes and may have subtle presentations [25]. Diabetes is associated with a twofold increased risk of being unable to perform daily physical tasks, such as walking, doing housework, or climbing stairs, and 1.6-fold greater risk of difficulties performing basic personal care, such as bathing, using the toilet, dressing, and eating. Diabetes complications, such as neuropathy, arthritis, and vascular disease, are contributors to physical disability in older people with diabetes [26, 27]. The Study of Osteoporotic Fractures has shown that diabetes also increases the risk of falls (odds ratio [OR] 2.78; 95% confidence interval [CI] 1.82 to 4.25). History of arthritis, musculoskeletal pain, depression, poor vision, and peripheral neuropathy are the main predictors of falling among older people with diabetes [28]. The risk of developing Alzheimer's disease or vascular dementia is twofold higher in older people with diabetes compared to age-matched people without diabetes [29]. In the Health, Aging, and Body Composition Study, older people (70–79 years old) with diabetes had an increased incidence of depression compared with those without diabetes (23.5% vs 19.0%, hazard ratio [HR] 1.31; 95% CI 1.07 to 1.61) [30].

Frailty

Frailty is a condition characterized by a reduction in physiological reserve and in the ability to resist physical or psychological stressors [31]. Its definition is largely based on the presence of three or more phenotypes (weight loss, weakness, decreased physical activity, exhaustion, and slow gait speed) [32]. Frailty is viewed as a wasting disease, with weight loss being one of its criteria. Undernutrition, which is common in older people, seems to be a risk factor for frailty. In the USA, ~16% of older persons living in the community are undernourished; these figures rise to 59% in long-term care institutions and 65% in acute care hospitals [33]. Sarcopenia or muscle mass loss is a component of frailty, which seems to be accelerated when diabetes is present. In a community study of 3153 people ≥65 years, appendicular lean mass loss in men with diabetes was twice that of men without diabetes (3.0% vs 1.5%) and in women with diabetes was 1.8 times that of those without diabetes (3.4% vs 1.9%) over four years of follow-up.

The mechanisms explaining these results may be related to reduced muscle protein synthesis as a result of lower testosterone and IGF-I and increased muscle protein breakdown caused by a higher rate of inflammation [34]. Diabetes also causes sarcopenia through the catabolic effect of insulin deficiency and by increasing intramyocellular lipid accumulation [35]. In another study, older people with type 2 diabetes had accelerated decline in leg lean mass, muscle strength, and longer sit to stand time compared to those with normoglycaemia [36]. Another factor related to malnutrition and frailty may be oral health. For example, optimal nutrition may not be maintained because of poor dentition, dry mouth, reduced taste sensation, palatability, and appetite change with increasing age [37].

Clinical presentation

Diabetes can be asymptomatic in up to 50% of older people [38]. However, when symptoms are present they are mostly non-specific and may be attributed to ageing. Non-specific symptoms, such as general malaise, fatigue, or lethargy, are common manifestation of diabetes in old age. Geriatric syndromes, such as falls and urinary incontinence, may be the first manifestation of diabetes. Symptoms may be atypical, for example anorexia rather than the typical polyphagia. The classic osmotic symptoms are usually less prominent because of the increased renal threshold for glucose (reducing the intensity of polyuria) and impairment of thirst sensation (reducing the intensity of polydipsia). Hyperosmolar hyperglycaemic state may be the presenting symptom, or diabetes may be first diagnosed during an acute illness or following a routine blood test (Box 72.3).

Box 72.3 Special considerations for the diagnosis and assessment of diabetes in old age: clinical presentation and diagnosis

- Fasting blood glucose may be normal in up to one-third of cases.
- Post-prandial or two-hour oral glucose tolerance test are more reliable.
- Glycated haemoglobin (HbA_{1c}) is specific but less sensitive as a diagnostic test.
- Symptoms may be absent in up to 50% of individuals with diabetes.
- Osmotic symptoms are less prominent.
- Other symptoms may be non-specific such as fatigue or lethargy.

Comprehensive geriatric assessment

Comprehensive geriatric assessment should be performed on initial diagnosis and annually, including assessment of:

- Cognitive function.
- Screening for depression.
- Assessment for frailty.
- Falls risk.
- Activities of daily living ability.
- Presence of urinary incontinence and chronic pain.
- Nutritional status.
- Medication taking and polypharmacy.
- Social circumstances.

Diagnosis

The diagnostic criteria for diabetes are the same irrespective of age (Chapter 2). Clinicians should be aware that fasting glucose concentration may be normal in the early stages of diabetes and is therefore less sensitive in diagnosing diabetes in old age; however, the two-hour oral glucose tolerance test (OGTT) appears to capture undiagnosed cases [39].

Since February 2011, glycated haemoglobin (HbA_{1c}) has been used as a diagnostic test for diabetes. However, although HbA_{1c} has high specificity (98.7%), its low sensitivity (46.8%) means that it can miss more than half of people with diabetes [40]. There are several pitfalls to using HbA_{1c} in older people. HbA_{1c} increases with age after adjustment for glucose, suggesting that non-glycaemic factors contribute to this increase. Furthermore, iron-deficiency anaemia, which is common in older people, is associated with an increase in HbA_{1c} independent of changes in blood glucose. Both of these factors will lead to overdiagnosis of diabetes in older people if HbA_{1c} is used in preference to glucose. The diagnosis should be confirmed by a second laboratory test in the absence of diabetes symptoms as for younger people.

Management

The phenotype of diabetes in old age is highly variable and affected by comorbidity, geriatric syndromes, and frailty. Therefore, the diabetes management should consider the heterogeneous nature of the diabetes and the complex needs of the individual. A comprehensive geriatric assessment should be performed after the initial diagnosis and annually, as age-related comorbidities may impair diabetes management (Figure 72.1). Hyperglycaemia should not be treated in isolation, but as part of a multifactorial intervention to reduce cardiovascular risk. Cardiovascular complications remain the main cause of mortality, accounting for 50–75% of all deaths in people with diabetes [41]. Management includes health behaviour modification and pharmacological interventions for hyperglycaemia and cardiovascular risk factors (Box 72.4).

Health behaviour modifications

Health behaviour modification includes changes in diet, weight reduction, smoking cessation (the single most effective means of reducing mortality [42]), and regular exercise to reduce visceral obesity and improve insulin sensitivity.

Ageing is associated with increased insulin resistance through the loss of skeletal muscle mass [12]. Muscle mass is dependent on a balance between muscle protein synthesis and breakdown; protein intake with exercise training synergistically increases skeletal muscle mass in older people. In one trial, protein supplementation for frail older people who were engaged in resistance training resulted in muscle hypertrophy, and increases in muscle strength, muscle mass, and performance [43]. A diet that is high in fibre and potassium and low in saturated fats and refined carbohydrates and salt may help achieve an ideal body weight as well as improving the lipid profile, significantly lowering blood pressure and reducing the overall cardiovascular risk [44]. A Mediterranean

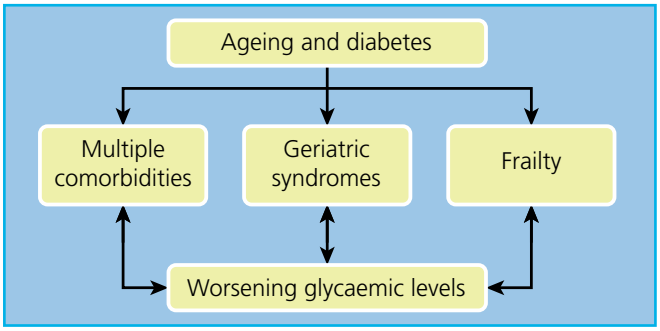

Figure 72.1 Interaction between the diabetes phenotype in old age and glycaemic levels. The interplay between ageing and diabetes leads to the development of the characteristic phenotype of diabetes in old age of multiple comorbidities, geriatric syndromes, and frailty, which in turn may lead to worsening of glycaemic levels setting a vicious circle.

Box 72.4 Management of cardiovascular risk factors in older people with diabetes

Health behaviour modifications
- Smoking cessation.
- Balanced diet with adequate nutrition, especially in frail individuals.
- Regular exercise.
- Weight loss in those who with overweight or obesity.

Hyperglycaemia
- Tight glycaemic targets in fit or newly diagnosed people.
- Conservative approach in frail persons.
- Avoid hypoglycaemia.

Hypertension
- A target systolic blood pressure of 140 mmHg is reasonable in fit individuals, but higher targets around 150–160 mmHg are appropriate in frail or very old (≥85 years) persons.
- Achieving target blood pressure is more important than the antihypertensive drug class used, and most people will need more than one drug to achieve the target.

Dyslipidaemia
- Statin therapy in older people with diabetes is beneficial and should be offered unless specifically contraindicated or life expectancy is limited by frailty and comorbidities.
- The routine use of fibrate or niacin in addition to statin is not recommended.

Aspirin
- Aspirin therapy should be considered selectively in older people with diabetes and high cardiovascular risk, but after assessment of their bleeding risk.

Multiple interventions
- Hypoglycaemia should not be treated in isolation, but as part of a multiple cardiovascular risk factor reduction.
- Statins and antihypertensive drugs have the largest effect in reducing cardiovascular events, followed by anti-diabetes agents and aspirin.

Reverse metabolism
- In frail individuals targets should be relaxed, because of the inverse relationship between cardiovascular risk factors and mortality.

diet, especially high intake of vegetables and fruits, was associated with reduced risk of frailty syndrome in older women with type 2 diabetes [45]. In the Diabetes Prevention Program, lifestyle intervention including modest weight reduction, a healthy low-fat diet, and regular exercise reduced the development of diabetes, and this beneficial effect persisted for up to 10 years after the end of the study, especially in older people (≥60 years) [46]. Additional benefits of exercise for older people may include increased muscle strength and improved walking balance. In the Look AHEAD (Action for Health in Diabetes) study, intensive lifestyle intervention significantly increased the probability of diabetes remission and improved other clinical outcomes [47]. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) also demonstrated a beneficial effect of exercise and nutrition on cognitive function in older people with diabetes [48].

Hyperglycaemia

Although the evidence in reducing microvascular disease by tight glycaemic management is established, there is ongoing debate about whether reducing blood glucose to near-normal levels results in lower cardiovascular events (Table 72.1) [49–52]. In frail older people, the benefit of blood glucose management diminishes in the presence of other comorbidities. In a decision analysis to assess the effects of baseline health status on prioritization of therapy, blood pressure management conferred a larger benefit than glucose at advanced ages (75–79 years) and the expected benefits of both therapies steadily declined as the level of comorbidity and functional impairment increased [53]. Therefore, in older people who are frail with multiple comorbidities and functional impairment, tight glycaemic targets may be more harmful by inducing hypoglycaemia. It is important to address individual goals of therapy, guided by the individual preferences, life expectancy, comorbidities, and the influences of therapy on quality of life. The advantages and disadvantages of anti-diabetes medications in older people are detailed in Table 72.2.

Hypertension

A target systolic blood pressure of ~140 mmHg is reasonable in older people with diabetes, as maintenance of a systolic pressure between 130 and 140 mmHg is associated with a reduction of adverse cardiovascular outcomes in older people with hypertension and diabetes. Tighter control is not warranted, however, as this may be associated with an increase in adverse events. In the International Verapamil SR-Trandolapril (INVEST) study, controlling systolic blood pressure to <130 mmHg was not associated with better cardiovascular outcomes than usual control of 130–140 mmHg in individuals aged ≥55 years, and it was associated with a non-significant increased risk of mortality (11.0% vs 10.2%; adjusted HR 1.20; 95% CI 0.99 to 1.45, p = 0.06) [54]. Tight blood pressure management (target <120 mmHg systolic) was also not beneficial and was associated with adverse outcomes in older people (40–79 years) with diabetes [55]. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) also had similar conclusions for older individuals, mean age 66 ± 7 years, of whom 57% were aged ≥65 years [56]. The more recent Systolic Blood Pressure Intervention Trial (SPRINT) showed that treating to a systolic blood pressure target of <120 mmHg compared with a target <140 mmHg resulted in significantly lower rates of fatal and non-fatal major cardiovascular events (HR 0.66; 95% CI 0.51 to 0.85) and death from any cause (HR 0.67; 95% CI 0.49 to 0.91) in older people ≥75 years of age. However, this study did not enrol older people with diabetes, stroke, heart failure, dementia, limited life expectancy of <3 years, unintentional weight loss (>10% of body weight during the preceding six months), or those residing in nursing homes. Individuals with these conditions may not benefit from such intensive treatment and may be at increased risk of adverse events [57].

Two meta-analyses of older people with diabetes did not show reduced myocardial infarction or mortality rates with systolic blood pressures <140 mmHg [58, 59]. In very old people (>80 years) the targets may be even more relaxed. The Hypertension in the Very Elderly Trial (HYVET), which included older people aged

Table 72.1 Summary of published trials evaluating the effect of lowering glucose concentration on cardiovascular outcomes.

	UKPDS follow-up [49]	ACCORD [50]	ADVANCE [51]	VADT [52]
Number of participants	3277	10 251	11 140	1791
Mean (SD) age (years)	62 (8.0)	62.2 (6.8)	66 (6.0)	60.5 (9.0)
Inclusion criteria	Newly diagnosed type 2 diabetes	Age 40–79 years with history of CVD or age 55–79 years with evidence of atherosclerosis, albuminuria, LVH, or two additional risk factors for CVD	Diagnosis of type 2 diabetes at ≥30 years of age or age ≥55 years or history of macro- or microvascular disease	Type 2 diabetes with inadequate response to maximum dose of oral agent or insulin therapy
History of cardiovascular disease	People with significant CVD excluded	35%	32%	40%
Duration of diabetes on entry (years)	Newly diagnosed	10.0	8.0	11.5
Cardiovascular outcome	Benefit	Harm	No benefit	No benefit
Hypoglycaemia intensive vs standard therapy (%)	2.4% for sulfonylurea, 1.8% for insulin, and 0.7% for standard therapy[a]	16.2 vs 5.1	53 vs 38	24.1 vs 17.6

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; CVD, cardiovascular disease; LVH, left ventricular hypertrophy; SD, standard deviation; UKPDS, UK Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.
[a] Only rates of severe hypoglycaemia were reported in the intervention phase of the study.

Table 72.2 Advantages and disadvantages of anti-diabetes medications in older people.

Medication	Advantages	Disadvantages
Sulfonylureas	Suitable for those with renal impairment or low risk of hypoglycaemia	Increased risk of hypoglycaemia and weight gain Long-acting sulfonylureas should be avoided
Metformin	Low risk of hypoglycaemia Cardiovascular benefit Weight neutral	Increased risk of lactic acidosis in those with renal impairment Heart failure, sepsis, and dehydration
Meglitinides	Short-acting Suitable for those with erratic eating pattern	Risk of hypoglycaemia and weight gain, but less than sulfonylureas
α-Glucosidase inhibitors	Low risk of weight gain and hypoglycaemia	Weak hypoglycaemic action Gastrointestinal side effects
Pioglitazone	Suitable for those with renal impairment Less risk of hypoglycaemia	Fluid retention Worsens heart failure Increases fracture risk and possibly bladder cancer
Dipeptidyl peptidase 4 (DPP-4) inhibitors	Low risk of hypoglycaemia Weight loss	Gastrointestinal side effects Dose mostly needs to be adjusted with renal impairment
Glucagon-like peptide 1 (GLP-1) receptor agonists	Low risk of hypoglycaemia Weight loss	Injectable Weight loss in frail individuals Not suitable in renal failure Nausea common Possible risk of pancreatitis
Sodium–glucose cotransporter 2 (SGLT-2) inhibitors	Low risk of hypoglycaemia Weight loss	Not suitable for frail older people with weight loss Heavy glucosuria increases risk of urinary tract infections, candidiasis, dehydration, and hypotension
Insulin	Effective Tailored rapidly to changes in need Improves quality of life.	High risk of hypoglycaemia and weight gain

≥80 years with sustained systolic blood pressure >180 mmHg, 7% of whom had diabetes, showed a significant 33.7% (HR 0.66; 95% CI 0.53 to 0.82, p < 0.001) reduction in cardiovascular events with a target blood pressure of 150/80 mmHg. However, the individuals included in HYVET were healthier than those in the general population, with a low baseline rate of known cardiovascular disease (11.5%), myocardial infarction (3.1%), or heart failure (2.9%). Therefore, the results may not apply to all older persons, especially those with multiple comorbidities or living in care homes [60]. In another community study of people aged ≥85 years there was a U-shaped relationship, with a systolic blood pressure of 164.2 mmHg (95% CI 154.1 to 183.8 mmHg) being associated with the lowest mortality, suggesting that the optimal systolic blood pressure for this age group could be >140 mmHg [61]. Thiazide diuretics, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers are reasonable first-choice agents, although higher doses of diuretics may worsen blood glucose and lipid profile. Most people will require more than one antihypertensive agent.

Dyslipidaemia

There are no large clinical trials of lipid-lowering interventions specifically in older people with diabetes. *Post hoc* analysis of the Heart Protection Study, which included participants with diabetes aged between 40 and 80 years, showed a significant 25% risk reduction of cardiovascular events [62]. The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) was designed for older people aged 70–82 years (10.5% had diabetes) with either pre-existing vascular disease (secondary prevention) or elevated risk of such disease due to smoking, hypertension, or diabetes (primary prevention), and showed 15% lower cardiovascular endpoints in the statin group [63]. A meta-analysis of 18 686 people with diabetes in 14 trials of statin therapy for primary prevention showed a similar 20% relative risk reduction in major adverse vascular outcomes in older (≥65 years) compared to younger (<65 years) people [64]. Therefore, the evidence for statin therapy is established for older people with diabetes up to the age of 80 years, whether they have no underlying heart disease (primary prevention) or already have established heart disease (secondary prevention).

In very old people (>80 years), cholesterol targets are unclear. A review of observational studies including 13 622 participants showed that low total cholesterol (<5.5 mmol/l) was associated with the highest mortality rate in those >80 years old [65]. The routine use of a fibrate or niacin in addition to statin therapy did not reduce cardiovascular events beyond the effects of statins and is not recommended [66, 67]. Cardiovascular prevention with statins emerges fairly quickly (within 1–2 years), suggesting that statins may be offered to nearly all older people with diabetes except those with very limited life expectancy. Chronological age *per se* should not exclude people from receiving therapy, but functional or biological age as well as the impact of long-term drug therapy on safety and quality of life should be considered.

Aspirin therapy

Aspirin reduces cardiovascular morbidity and mortality in people with a history of cardiovascular disease [68]. However, evidence for aspirin use in primary cardiovascular risk prevention is still unclear. A meta-analysis of aspirin treatment as primary prevention in people with diabetes demonstrated a trend towards a 10% reduction in cardiovascular events, but this needs to be balanced against an increased risk of haemorrhage [69]. A more recent meta-analysis has shown a statistically significant protective effect of aspirin and a moderate level of confidence for the administration for the primary prevention in diabetes, particularly in older individuals (age ≥60 years) [70]. Presence of diabetes *per se* does not justify aspirin use. However, most older people with diabetes have a high burden of cardiovascular risk factors and are likely to benefit from aspirin therapy. Therefore, aspirin use should be considered selectively in older individuals with diabetes and high cardiovascular risk after assessment of the risk of bleeding.

Multiple risk intervention

Cardiovascular risk factors tend to cluster in what is known as the *metabolic syndrome*. Both age and diabetes increase the prevalence of the metabolic syndrome. In a Norwegian study, the prevalence increased from 11.0% in men aged 20–29 years to 47.2% in men aged 80–89 years, and from 9.2% to 64.4% for women in the corresponding age groups [71]. In a population-based study of 5632 white

European people (65–84 years old), the prevalence was 64.9% and 87.1% in men and women with diabetes, respectively, compared to 25.9% and 55.2% in men and women without diabetes [72]. Although metabolic syndrome is postulated as a risk factor for cardiovascular disease, in a prospective study of 1025 older people aged 65–74 years [73] and an analysis of the outcomes of two prospective studies in people aged over 60 years [74], the metabolic syndrome was shown to be a marker of cardiovascular disease, but did not enhance risk prediction above and beyond the risk associated with its individual components.

Multifactorial interventions are appropriate and show that the use of statins and antihypertensive drugs has the largest effect in reducing cardiovascular events, with anti-diabetes agents and aspirin the next most important interventions [75]. More effort is needed to optimize this comprehensive approach, as many older people do not receive this level of care [76].

Reverse metabolism

In frail older people, the power of traditional cardiovascular risk factors including hypertension, dyslipidaemia, and hyperglycaemia to predict risk of cardiovascular disease seems to diminish with age, leading to a paradoxical relationship [77]. The more commonly proposed explanations include the association of low body weight and low cholesterol with increased protein energy malnutrition and increased inflammation associated with frailty [78]. In a study of 331 very old people (mean age 85 ± 7 years), low body mass index, low blood pressure, low total and high density lipoprotein (HDL) cholesterol, and high insulin sensitivity in individuals without diabetes predicted total mortality, indicating a *reverse metabolism* that is probably attributable to malnutrition and chronic disorders, which have a negative impact on survival [79]. Low albumin (a marker of malnutrition) and high C-reactive protein (a marker of inflammation) were associated with these cardiometabolic factors, limiting their prognostic value for cardiovascular risk in older people [79]. It is important to recognize that many older people with diabetes are frail and the expected benefit of tight metabolic management declines as morbidity and functional impairment increase, thus functional status and level of comorbidity are important factors in assessing risk [53].

Special considerations in old age

Hypoglycaemia

Hypoglycaemia is commoner in older people with diabetes because of the associated comorbidities, geriatric syndromes, polypharmacy, long duration of diabetes, and the increased prevalence of hepatic and renal dysfunction (Box 72.5). Although there is a paucity of data about the incidence of hypoglycaemia in older people, the reported incidence of hypoglycaemia varies in the literature, owing to differences in the definition used and the age of the populations studied. In a US retrospective population-based study of 19 932 Medicaid individuals aged ≥65 years, the incidence of severe hypoglycaemia was 1.23 episodes per 100 person-years for people treated with sulfonylureas and 2.76 episodes per 100 person-years in those treated with insulin [80]. However, the strict definition of severe hypoglycaemia (an episode leading to fatal outcome or hospital admission) may have underestimated the true frequency of events. Also, the data collection was conducted before the publication of the evidence for the benefit of tight glycaemic management in type 2 diabetes in 1998 [81].

Box 72.5 Hypoglycaemia in older people with diabetes

Incidence
- Increased in old age due to multiple comorbidities, undernutrition, polypharmacy, long duration of diabetes, and renal or hepatic impairment.

Difficult recognition
- Non-specific symptoms.
- Misdiagnosed for stroke, vertigo, or visual disturbance.
- Misinterpreted as dementia-related symptoms, such as agitation or behaviour change.
- Atypical presentation, e.g. confusion or passive delirium.
- Little warning or unawareness of autonomic symptoms.
- People with dementia are unable to communicate their feelings or symptoms.

Consequences
- Acute events such as cardiac arrhythmias or stroke.
- Chronic consequences such as mental and physical dysfunction.

The subsequent trends towards tighter glycaemic targets have resulted in more frequent hypoglycaemic episodes, with insulin becoming the second commonest medication associated with adverse events reported to the US Food and Drug Administration, with a threefold increase in reported events from 1998 to 2005 [82]. Insulin was the second most frequent medication associated with emergency department visits in older people ≥65 years; 95.4% of episodes were related to hypoglycaemia, 24.1% involved loss of consciousness or seizure, and 25.1% required hospitalization [83]. More recently, in a prospective study involving 3347 people, median age 66.1 years, from DiaRegis, a multicentre registry of people with diabetes in Germany, the annual incidence of hypoglycaemia of any severity was 14.1% [84].

Although hypoglycaemia incidence is difficult to estimate accurately, it is likely to be higher in older than younger people. In a prospective observational study of 3810 people in primary care, 11% of participants reported at least one episode of hypoglycaemia of any severity in a 12-month period. Older people (≥70 years) reported more episodes than younger (<60 years) people (12.8% vs 9.0%, $p < 0.01$). Significant differences were also seen for symptomatic episodes without a need for help (9.2% vs 5.6%) and symptomatic episodes with a need for medical assistance (0.7% vs 0.1%) [85]. In care homes the incidence of hypoglycaemia is likely to be much higher than in a community setting, reaching up to 41.9% in one study over a one-year period (median 2, range 1–10 episodes/person/yr) because of the higher levels of comorbidities [86].

Recognition

Although hypoglycaemia in older people with diabetes is common, its recognition and diagnosis can be difficult. For example, owing to the predominance of neurological rather than autonomic symptoms, hypoglycaemia may present with symptoms such as dizziness or visual disturbance, resulting in misdiagnosis [87]. Another diagnostic challenge is the similarity in the clinical presentation of hypoglycaemia with that of dementia, where people may present with agitation, increased confusion, or behavioural

changes. Furthermore, symptoms of hypoglycaemia tend to be less specific with increasing age. In a survey of hypoglycaemia symptoms perception by older people with diabetes (age 82.3 ± 3.9 years) attending an outpatient clinic, the majority of respondents reported no diabetes-specific symptoms of being generally unwell when their blood glucose level dropped, making the recognition of hypoglycaemic episodes more difficult for healthcare professionals [88]. This was also demonstrated in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, with non-specific fatigue or weakness being the commonest symptoms of hypoglycaemia experienced by the participants (mean age 62.2 ± 6.8 years) [89]. In older people the threshold of autonomic symptoms of hypoglycaemia occurs at a lower blood glucose concentration while cognitive dysfunction occurs at a higher level compared with younger adults. Therefore, autonomic and neurological symptoms occur almost simultaneously with little warning [90]. This is referred to as *impaired awareness of hypoglycaemia* [91]. Subclinical hypoglycaemia or episodes with fewer symptoms may further reduce awareness, leading to a vicious cycle whereby one episode of hypoglycaemia can induce further hypoglycaemia [92]. Therefore, many episodes of hypoglycaemia may be unrecognized and under-reported by both people with diabetes and healthcare professionals, and subsequently the frequency is likely to be underestimated.

Consequences

Older people with diabetes are likely to be at a higher risk of the adverse consequences of hypoglycaemia because of the increased prevalence of comorbidities, undernutrition, and polypharmacy compared with younger people [93]. Severe hypoglycaemia may lead to serious acute vascular events, such as stroke, myocardial infarction, acute cardiac failure, and ventricular arrhythmias [94, 95]. The morbidity attributed to recurrent episodes of hypoglycaemia is associated with silent and chronic complications, which could lead to significant physical and cognitive dysfunction and eventually to frailty, disability, and increased mortality. In a Taiwanese study of 234 residents aged 77.5 years living in long-term care facilities, of whom 35.5% had diabetes, hypoglycaemia was associated with disability and reduced function. Functional status was worse in those who experienced hypoglycaemia in comparison with those with no history of hypoglycaemia (mean Barthel Index score 22.5 vs 38.2). Complete dependence, defined as Barthel Index score <30, was also commoner in people with hypoglycaemia (69.2% vs 50%) [86].

The burden of hypoglycaemia leading to hospitalization is higher in old age and may contribute to increased frailty and reduced quality of life. In a US study of 33 492 people with diabetes aged ~60 years, accidents resulting in hospital visits occurred in 5.5% of those with hypoglycaemia compared to 2.8% of those without. Hypoglycaemia was associated with significantly increased hazards for any accident (HR 1.39; 95% CI 1.21 to 1.59, $p < 0.001$), accidental falls (HR 1.36; 95% CI 1.13 to 1.65, $p < 0.001$), and motor vehicle accidents (HR 1.82; 95% CI 1.18 to 2.80, $p = 0.007$) after adjustment for baseline characteristics. In an age-stratified analysis, the risk of falls was twice as high among older people, ≥65 years, compared with younger individuals, and hypoglycaemia was significantly associated with a greater than 50% increase in the hazard of falls (adjusted HR 1.52; 95% CI 1.18 to 1.95) [96]. Hypoglycaemia also increases the risk of fractures, which may lead to disability and frailty. In a retrospective observational study of 361 210 Medicare-covered people with diabetes ≥65 years old, those with hypoglycaemic events had a significantly higher proportion of fall-related fractures compared to those without hypoglycaemia (5.24% vs 2.67%, $p < 0.001$). Hypoglycaemic events increased the risk of falls and fractures by 70% (OR 1.7; 95% CI 1.58 to 1.83) [97].

Dementia

Progressive decline in cognitive function leading to dementia is common in older people with diabetes. Persistent hyperglycaemia increases the risk of cerebrovascular disease by inducing inflammation, endothelial dysfunction, oxidative stress, and insulin resistance, leading to an increased incidence of vascular dementia [98]. Moreover, accelerated brain ageing from altered amyloid metabolism, increased protein glycation, and direct cerebral glucotoxicity may explain the increased incidence of Alzheimer's dementia [99]. Structural changes in the brain have been noted with diabetes and dementia. For example, cerebral atrophy and hippocampal atrophy are reported more frequently in older people with diabetes and contribute to cognitive dysfunction, especially impairment in immediate memory [100]. It seems that brain insulin resistance increases in Alzheimer's disease, suggesting that Alzheimer's may be caused by a cerebral manifestation of diabetes.

Risk

Among people with diabetes, the relative risk of Alzheimer's disease is 1.56 (95% CI 1.41 to 1.73), while vascular dementia is increased 2.27-fold (95% CI 1.94 to 2.66) and all types of dementia by 1.73-fold (95% CI 1.65 to 1.82) compared to those without diabetes [101]. In a prospective study of older people (>60 years) with diabetes, age, microvascular disease, diabetic foot, cerebrovascular disease, cardiovascular disease, acute metabolic events, depression, and education were used to develop a risk score for dementia. Over 10 years, the risk of developing dementia was 5.3% (95% CI 4.2 to 6.3) for the lowest score (−1) and 73.3% (95% CI 64.8 to 81.8) for the highest (12–19) sum scores [102]. The presence of diabetes also accelerates mortality rate in people with dementia. In a retrospective Australian study, the mortality rate for people with diabetes and dementia was almost twice that of those with dementia but without diabetes (HR 1.9; 95% CI 1.3 to 2.9) [103].

Implications

Older people with diabetes and dementia experience difficulties in performing self-care tasks. In a community-based study of 1398 people with diabetes aged 70 years, diabetes self-care tasks decreased as cognitive impairment increased, with exercise and diet adherence being the most strongly associated with cognitive impairment [104]. The combination of diabetes and dementia is likely to be associated with an increased incidence of treatment adverse events, such as severe hypoglycaemia [105]. Due to erratic eating patterns associated with dementia, older people with diabetes are also at risk of malnutrition, dehydration, and worsening diabetes control. Carers of people with diabetes and dementia face extraordinary challenges to care for both conditions, especially in people who develop behaviour changes. Their needs should be identified early to allow for greater support from the healthcare system.

Management

Although there is an association between hyperglycaemia and cognitive dysfunction, intensive glycaemic management does not prevent a decline in mental function [106]. Once dementia develops diabetes self-care deteriorates, and so clinicians need to check for cognitive dysfunction if declining self-care occurs. Clinicians

Box 72.6 Dementia in older people with diabetes

Screening
Should be performed annually or earlier if one of the following is observed:
- Less medication taking.
- Forgetfulness in how to handle insulin injections.
- Forgetting how to recognize or treat hypoglycaemia.
- Difficulties in how to interpret blood glucose results or make decisions regarding adjusting insulin doses.
- Declining general self-care.
- Erratic eating pattern and missing meals.
- Not following dietary requirements.
- Recurrent unexplained hypoglycaemia.

Screening tool (Mini-Cog)
Ask the person to repeat three items such as lemon, key, and balloon, then provide a clock face:
- Ask the person to draw the numbers of the clock face.
- Ask the person to draw the hands of the clock to show the time as ten to three.
- Ask the person to recall the three items.

Give one mark for each task performed and for each item remembered. A score of 0–3 out of a maximum of 5 defines cognitive impairment.

should also be aware that dementia may be associated with language impairment, disorientation, and personality changes that may mimic the symptoms of hypoglycaemia [107]. The Mini Cog test is a simple screening tool for dementia that has a sensitivity of 86.4% (95% CI 64.0 to 96.4%) and a specificity of 91.1% (95% CI 85.6 to 94.6%) and takes only three minutes to perform [108].

Older people with diabetes and dementia have complex needs because of increased dependency and unpredictable behavioural changes as the decline in cognitive function continues. For example, hydration should be maintained because of impaired thirst sensation to avoid risk of volume depletion and hyperglycaemic crises. In people treated with insulin, the new class of long-acting insulin analogues may be a good option as they reduce the risk of hypoglycaemia and can be conveniently injected once daily [109]. People who have erratic eating patterns and unpredictable caloric intake could be managed with a regimen where short-acting insulin analogues are administered only after meal consumption, thus reducing the risk of hypoglycaemia if a meal is missed or only partly consumed (Box 72.6).

Hypoglycaemia–dementia interaction

The brain is highly dependent on glucose for its metabolism and is particularly vulnerable to hypoglycaemia, especially in older people. After each hypoglycaemic episode major cognitive changes occur, leading to post-hypoglycaemic encephalopathy. Repeated episodes of hypoglycaemia may contribute to cognitive dysfunction and the relationship appears to be bidirectional. History of severe hypoglycaemia increases risk of cognitive dysfunction [110] and cognitive dysfunction increases risk of hypoglycaemia [111]. Therefore, recurrent hypoglycaemia may be associated with impaired cognitive function and development of dementia. In a retrospective study of 16 667 older people with diabetes, mean age 65 years, the risk of dementia increased by 26% (HR 1.26; 95% CI 1.10–1.49), 80% (HR 1.80; 95% CI 1.37 to 2.36) and 94% (HR 1.94; 95% CI 1.42 to 2.64) in those with a history of one, two, and three or more severe hypoglycaemic episodes (defined as hypoglycaemia needing hospital admission or emergency department visit), respectively independent of glycaemic levels, medications, and comorbidities. The attributable risk of dementia was 2.39% (95% CI 1.72 to 3.01) per year in people with compared with those with no history of hypoglycaemia [110].

In an observational cohort study of 302 participants with diabetes, mean age 75.7 ± 4.6 years, a cross-sectional association between severe hypoglycaemia and cognitive function was observed. People with dementia (16% of participants) or cognitive impairment (14%) were significantly more likely to have been hospitalized with hypoglycaemia than people with normal cognitive function (3.8%), $p = 0.004$ [112]. A prospective association between historical hypoglycaemia and cognitive decline in a subsample of the participants without dementia was not found. However, the prospective phase of this study was limited by the small number of participants (n = 205) and short duration of follow-up (18 months), which may have limited the power to detect any association between incident hypoglycaemia and cognitive dysfunction [105]. More recently, in the Edinburgh population-based cross-sectional study of 1066 people with type 2 diabetes, mean age 67.9 ± 4.2 years, self-reported history of severe hypoglycaemia was associated with poorer late life cognitive ability. Those who reported at least one episode of severe hypoglycaemia demonstrated poorer performance on tests of verbal fluency (34.5 vs 37.3, p = 0.02), digit symbol testing (45.9 vs 49.9, p = 0.002), letter–number sequencing (9.1 vs 9.8, p = 0.005), and trail making ($p < 0.001$) independent of diabetes duration, vascular risk factors, or vascular complications. These associations persisted after adjustment for estimated prior cognitive ability, suggesting that the association may be attributable to an effect of hypoglycaemia on age-related cognitive decline [113]. A linear relationship was observed between poorer general cognitive ability and increasing frequency of severe hypoglycaemia over the year preceding cognitive testing, supporting results of earlier studies.

Management of diabetes

Glycaemic targets

Glycaemic targets should be individualized taking into consideration overall health and life expectancy.

Fit older people
For healthier older people with low prevalence of cardiovascular risk factors, especially those with a new diagnosis of diabetes, tight glycaemic targets with an HbA_{1c} around 53 mmol/mol (7%) are reasonable, as these are likely to reduce diabetes complications [49], while persistent hyperglycaemia is associated with increased risk of falls [114] and mortality [115] regardless of the associated comorbidities.

Frail older people
For frail older people or those with established cardiovascular disease, a safer target around 58–64 mmol/mol (7.5–8.0%) is appropriate. The presence of multiple comorbidities is a potential competitor for the benefit of tight glycaemic levels in this population. In a decision analysis to assess the effects of comorbid conditions and functional impairment, the expected benefits of tight glycaemic levels

(HbA_{1c} 53 versus 63 mmol/mol; 7.0% vs 7.9%) declined steadily as the level of comorbidities and functional impairment increased. One to two points were allocated for each comorbidity, according to severity, to create a mortality index score. In people aged 60–64 years with new-onset diabetes, the quality-adjusted days declined from 106 (95% CI 97 to 117) days to 44 days (range 38–50) with three additional points in mortality index score, and to eight days (range 5–10) with seven additional index points [53].

Very frail older people

For very frail older people, residents in nursing homes, and those with limited life expectancy, a target HbA_{1c} of 64–75 mmol/mol (8.0–9.0%) is suitable. Tight glycaemic targets in this population may be harmful by inducing hypoglycaemia and reducing quality of life. However, higher HbA_{1c} (>75 mmol/mol; >9.0%) is associated with increased mortality [116]. Targets in this population should focus on short-term day-to-day blood glucose management rather than long-term HbA_{1c}, to avoid both hyperglycaemia, which may lead to lethargy, dehydration, visual impairment, and infections, and hypoglycaemia, which may lead to falls and confusion (Figure 72.2).

Polypharmacy

Clinical guidelines are largely disease specific, age neutral, and driven by numerical surrogates, such as HbA_{1c} or blood pressure, but do not necessarily consider hard endpoints and outcomes relevant to older people, such as physical function, disability, or quality of life [117]. Indiscriminate application of guidelines may lead to overtreatment and polypharmacy (taking >4 drugs), with potential harm and increased hospitalization in older people. For example, older people are more liable to experience adverse effects of antihypertensive medications, such as renin angiotensin system blockers leading to acute kidney injury, hyperkalaemia, or hypotension with further deterioration of renal function, especially in those with existing chronic kidney disease. Withdrawal of these drugs in older people (mean age 73.3 years) with stage 4 and 5 chronic kidney disease improved kidney function [118]. A gradual decrease of blood pressure is an essential strategy in treating older people with hypertension to avoid an accelerated blood pressure drop with subsequent falls. Blood pressure should be measured both lying and standing and the individuals asked about orthostatic symptoms to avoid orthostatic hypotension. It is important to realize that the presence of orthostatic symptoms, such as dizziness, lightheadedness, or faintness, is associated with an increased risk of falls (OR 8.21; 95% CI 4.17 to 16.19) rather than orthostatic hypotension *per se* [119].

Avoidance of hypoglycaemia is essential, especially in those with impaired kidney or liver function that delays the clearance of anti-diabetes medications [120]. Glycaemic goals should be regularly reviewed and anti-diabetes medications adjusted with increasing age, especially in those with the onset of cognitive impairment or frailty. Declining weight, malnutrition, and frailty may lead to a reduced need for anti-diabetes medications while increasing the risk of hypoglycaemia. Anti-diabetes medications have been safely withdrawn in a cohort of frail nursing home older people with type 2 diabetes, mean age 84.4 ± 6.8 years [121], and in another group in the community, mean age 86.5 ± 3.2 years, attending outpatient clinics without a deterioration of their glycaemic levels [122]. The main characteristics of these individuals were significant weight loss, increased comorbidities including dementia and polypharmacy, with recurrent hypoglycaemia [122]. Therefore, people with these criteria appear to be suitable candidates for a trial of anti-diabetes medication withdrawal. Higher doses of statins should be avoided in frail older people, who may be more susceptible to drug-related myopathy. Non-steroidal anti-inflammatory drugs should be used carefully in older people with diabetes, especially those with chronic kidney disease, because of the increased risk of acute kidney injury. Polypharmacy is common: in a British care home study, 84% of residents with diabetes were taking >4 drugs, with a high proportion (59%) of residents prescribed drugs for cardiovascular disease prevention. This may be inappropriate in this disabled population with limited life expectancy, as polypharmacy leads to increased risk of drug errors, hypoglycaemia, and hospitalization. Therefore, regular medication review of care home residents with diabetes should be undertaken, as it has the potential to reduce costs and minimize adverse drug reactions [123].

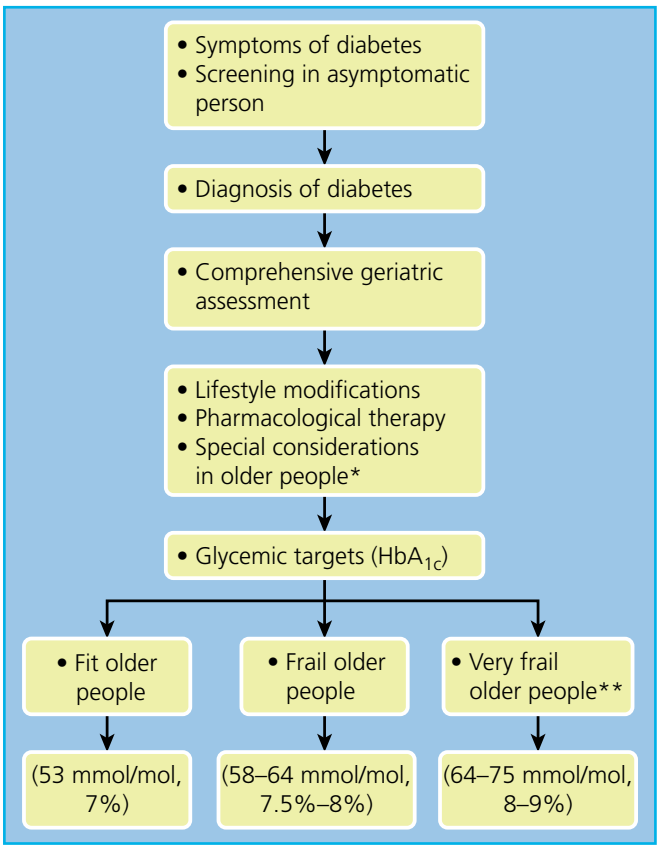

Figure 72.2 Diabetes diagnosis, management, and glycaemic targets. *Considerations such as risk of hypoglycaemia, dementia, polypharmacy, and residents in care homes. **In very frail older people with limited life expectancy, short-term targets of blood glucose >4 but <15 mmol/l are more important than the long-term glycated haemoglobin (HbA_{1c}) target.

Care homes

Care home residents with diabetes are likely to be frail, with multiple comorbidities and limited life expectancy. Therefore short-term glycaemic targets with minimal diabetes-related interventions are important to maintain quality of life. Maintaining a random blood glucose between 4 and 15 mmol/l (70–270 mg/dl) is reasonable, as blood glucose outside this range is likely to be symptomatic and result in cognitive changes [124]. Maintaining blood glucose in this *comfort zone* may ensure *comfort care*, avoiding both hyperglycaemia

Box 72.7 Recommendation for care of older people with diabetes in care homes

On admission to care home
- Each resident should be screened for the presence of diabetes.
- Each resident with diabetes should have assessment for functional loss and interventions in place to delay disability.

During their stay at a care home
- Residents should be regularly reviewed for the presence of hypoglycaemic symptoms, especially for those on insulin or sulfonylureas.
- Resident with diabetes should have optimal blood pressure and blood glucose regulation to help maintain cognitive and physical performance.

Good clinical practice in care homes
- All residents should have an annual screen for diabetes.
- Each resident with diabetes should have an individualized diabetes care plan.
- Care homes with diabetes residents should have an agreed diabetes care policy or protocol that is regularly audited.
- Diabetes education and training courses should be available to care home staff.
- A risk–benefit approach should be adopted in the management of residents with diabetes in terms of medications, metabolic targets, and extent of performing investigations, with a focus on enhancing quality of life, maintaining functional status, and avoiding hospital admission for diabetes-related complications.

and hypoglycaemia, thereby reducing malaise and improving mental function and general well-being [125] (Box 72.7).

Care plans

Care homes should have a policy for diabetes care, including diabetes screening for residents on admission and an individualized care plan for residents. Care plans should be tailored to individual needs and take into consideration the individual's values, preferences, life expectancy, comorbidities, and the impact of diabetes management (polypharmacy, glucose monitoring) on quality of life. Medications should be reviewed to switch those taking longer-acting sulfonylureas to shorter-acting agents and polypharmacy reviewed regularly. Screening for complications relevant to older people, such as cognition, physical function, and depression, should be included in their annual review.

Nutrition

Nutritional guidelines should not be too restrictive but tailored to be healthy and to reflect personal preferences. Individuals are free to exercise personal choices with respect to food selection. Diabetes treatment is then adjusted accordingly. The aims of nutritional intervention include maintenance of healthy body weight and avoidance of malnutrition.

Holistic approach

An individualized, holistic care plan is recommended to address care home residents' complex needs [126]. Residents with diabetes should have an annual comprehensive foot examination to identify risk factors for ulcers and amputations. Podiatry input should be available regularly. Residents with diabetes should have an initial comprehensive eye examination and annually thereafter. Domiciliary optometric services may be an option for residents who are not able to travel.

Education

As older people are at increased risk of hypoglycaemia [87, 95] and may tolerate low blood glucose with no specific symptoms due to diminished autonomic response, it is important that residents and care home staff are educated to recognize the symptoms and treat hypoglycaemia. In a study that delivered a diabetes educational programme to care home staff, staff knowledge improved and was retained at 12 months, and led to improved quality of care up to a year after the intervention [127].

Conclusion

Ageing is associated with increased insulin resistance, due to decreased muscle mass, increased visceral fat, and decreased insulin secretion, because of diminished β-cell mass and function, leading to glucose intolerance and diabetes in genetically susceptible individuals. Through population ageing and increased life expectancy, diabetes is increasingly becoming a disease of older age. The phenotype of diabetes in old age is characterized by an increased prevalence of multiple comorbidities, geriatric syndromes, and frailty. Therefore, the assessment of older people with diabetes on diagnosis and annually thereafter should be comprehensive and include screening for these syndromes, especially cognitive and physical dysfunction. Older people are a highly heterogeneous population, ranging from a fit person living in the community to a frail individual with multiple comorbidities living in a care home. Management should therefore be individualized, with variable metabolic targets from optimal glycaemic levels in fit individuals to a conservative approach in frail ones. More attention should be focused on optimal management of undernutrition in frail older people by improving nutrition and physical activity to maintain muscle mass and improve overall function. Quality of life should be at the centre of the management plan.

Future perspectives

Although tight glycaemic levels will continue to be the aim for older fit and independent people with diabetes, these are not suitable for those who are frail and at a high risk of side effects due to polypharmacy [128]. A new approach to defining glycaemic targets based on the level of function has recently been introduced by the International Diabetes Federation and represents the first comprehensive guidance in this area [129].

There is a need for clinical trials specifically designed for older people with diabetes to explore the real benefit of glycaemic management in this diverse group. Comprehensive geriatric assessment including physical and mental health assessment will continue to be essential in view of the epidemiological shift of diabetes towards older age. Frailty and geriatric syndromes are emerging as complications in older people with diabetes and will need interventions beyond glycaemic management. There remains a lack of

intervention studies that reduce disability and improve quality of life in older people with diabetes. A focus on improvements in function may be of greater clinical relevance in frail older people with diabetes than metabolic targets alone. The MID-Frail study will evaluate the clinical, functional, social, and economic impact of a multimodal intervention (resistance training exercise, diet, and education) in frail and pre-frail participants aged ≥70 years with type 2 diabetes compared with usual clinical practice [130]. This may have an impact on reducing functional decline, promoting independence, and maintaining quality of life.

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73 Diabetes at the End of Life

Trisha Dunning[1,†] and June James[2]

[1] Formerly of Deakin University, Geelong, Victoria, Australia

[2] Leicester Diabetes Centre, Leicester, UK

Key points

- Death is an expected part of life and therefore end-of-life care is a vital aspect of holistic diabetes care.
- Diabetes often contributes to the cause of death, but diabetes as the main cause of death is under-reported on death certificates, with most deaths attributed to other causes such as cardiovascular disease, heart failure, chronic kidney disease, and cancer.
- It is estimated that 6.7 million people with diabetes aged 20–79 died in 2021. Diabetes was the ninth leading cause of death worldwide in 2019.
- People are approaching their end of life when they are likely to die within the next 12 months.
- Generic end-of-life guidance applies to people dying with diabetes.
- Glycaemic targets may be relaxed in the last year of life; glycated haemoglobin (HbA_{1c}) may not be required during this time. The blood glucose should be kept between 6 and 15 mmol/l (110–270 mg/dl).
- Hypoglycaemia in people taking insulin or oral hypoglycaemic agents is predictive of mortality.
- Insulin treatment must not be stopped in dying people with type 1 diabetes to prevent ketoacidosis, which can be a diabetes-specific cause of death.
- People with diabetes should document their values and end-of-life care preferences in an Advance Care Directive/Plan while they can make autonomous decisions. This aids end-of-life care decision making by healthcare professionals and the family.
- Healthcare professionals should have initial and regular training and competency assessment in end-of-life care.

Dying with diabetes

Diabetes is common, with an overall global prevalence in adults of 537 million people in 2021. The prevalence is expected to increase to 643 million by 2031 and 783 million by 2045 [1]. The prevalence is higher in older people: 10–30% of people in Europe of pensionable age have diabetes and 25% of care home residents in the UK have diabetes [2].

Although survival with diabetes has been improving, people with diabetes still have reduced life expectancy compared with the general population, especially those in low- and middle-income countries and those living in remote areas [1]. The UK National Diabetes Audit shows there are 500 premature deaths per week in the UK [3].

China and India had the most recorded number of deaths attributed to diabetes in 2021, but these countries also have the largest populations. The highest proportion of total deaths associated with diabetes are Singapore (29%) and Pakistan (29%). Russia and Czechia have the lowest proportion of deaths, each with approximately 1% of total deaths. Diabetes is said to have been responsible for 416 000 deaths in Africa in 2021 [1]. In the USA, diabetes and its complications were the seventh leading cause of death in 2019, accounting for 87 647 deaths [4]. In Australia, diabetes was the most significant underlying cause of death in over 3300 deaths between 1985 and 2017, with higher death rates in Aboriginal and Torres Strait Islander people, especially women [5].

These data may underestimate death rates because only 35–40% of recorded deaths in people known to have diabetes included diabetes on their death certificate and only 10–15% had it listed as the underlying cause of death [6]. There are apparent variations in mortality related to diabetes across the world, but generally as the prevalence increases so do deaths, especially if diabetes is not well managed from diagnosis [7].

Causes of death attributed directly to diabetes include ketoacidosis, severe hypoglycaemia, and hyperosmolar hyperglycaemic state. These deaths account for only a minority of all diabetes-related deaths [8]. In high-income countries, the premature mortality in people with diabetes is predominantly caused by a higher prevalence of cardiovascular disease, particularly heart failure, which accounts for 75% of all deaths and is associated with a 10-year reduction in life expectancy [1]. The next most common causes of death are chronic kidney disease [7] and cancer [9]. Individuals with type 2 diabetes are at increased risk of developing certain cancers because both conditions share many of the same risk factors, including ageing, obesity, physical inactivity, high-fat–high-sugar diets, alcohol, and smoking [9, 10].

[†] Deceased on 14 October 2021.

Textbook of Diabetes, Sixth Edition. Edited by Richard I.G. Holt and Allan Flyvbjerg.
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It follows that healthcare professionals working with adults will encounter people with diabetes who are dying in various care settings. They should know how to discuss end-of-life issues with their patients and help them document advance care directives or plans to address their needs at the end of life. Significantly, initiating palliative care early improves outcomes and this care can be incorporated with usual diabetes care [11].

End of life

Palliative medicine is a surprisingly young specialty even in high-income countries, probably because death has been regarded as a failure of medical care. This attitude began to change following the pioneering work of people such as Dame Cicely Saunders and the International Declarations about the rights of the dying person. In 1976 the Parliamentary Assembly of the Council of Europe resolved that 'The prolongation of life should not in itself constitute the exclusive aim of medical practice, which must be concerned equally with the relief of suffering' [12].

The principles of care at the end of life apply to everyone who is terminally ill and have been articulated in numerous publications, which have themselves been revised in line with evidence and experience (Table 73.1) [13]. The sensitive application of such principles tailored to the individual and supplemented by excellent communication with them and their families and among healthcare professionals is likely to result in the best possible outcome under the circumstances, which is a *good death* for the individual.

Early identification of people entering the end-of-life phase

Although self-evident, end-of-life care cannot start until healthcare professionals realize the individual is dying and communicate that they are in the terminal phase of life to all relevant people. Recognizing when the person is at their end of life is not intuitive, particularly when medical and nursing staff have been providing active management intended to achieve a cure. Guidance has been produced to assist healthcare professionals to recognize deterioration and the terminal stage of life.

Table 73.1 Key principles of end-of-life care in people with diabetes.

Provision of a painless and symptom-free death
Tailor glucose-lowering therapy and minimize diabetes-related adverse treatment effects
Avoid metabolic decompensation and diabetes-related emergencies such as: • frequent and unnecessary hypoglycaemia • diabetic ketoacidosis • hyperosmolar hyperglycaemic state • persistent symptomatic hyperglycaemia
Avoidance of foot complications in frail, bed-bound people with diabetes
Avoidance of symptomatic clinical dehydration
Provision of an appropriate level of intervention according to stage of illness, symptom profile, and respect for dignity
Supporting and maintaining the empowerment of the individual person (in their diabetes self-management) and carers to the last possible stage.

Source: Modified from James et al. 2021 [13]. Reproduced by permission.

The General Medical Council UK [14] states that individuals are approaching the end of life when they are likely to die within the next 12 months. This includes those whose death is imminent (expected within a few hours or days) and those with:

- Advanced, progressive, incurable conditions.
- General frailty and coexisting conditions that mean they are expected to die within 12 months.
- Existing conditions if they are at risk of dying from a sudden acute crisis in their condition, e.g. dementia and chronic diseases such as diabetes, where each crisis depletes the individual's overall reserves.
- Life-threatening acute conditions caused by sudden catastrophic events.

Research suggests that people prefer a death free of pain and discomfort to a longer life; however, these thoughts and feelings may differ according to cultural beliefs [15]. People are more likely to have their preferred death if they document a clear advance care plan based on their values. Values are those things that give meaning and purpose to their lives [13, 15].

The Gold Standards Framework for end-of-life care, developed in the UK [16], identified triggers that can help healthcare professionals determine whether the individual is nearing their end of life (Box 73.1).

The Gold Standards Framework also defines four main stages of end of life [16]:

1. Stable from diagnosis (usually lasting years).
2. Unstable, advanced disease (usually lasting months).
3. Deteriorating, exacerbations (usually lasting weeks).
4. Last days of life pathway (usually lasting days).

This model was adapted in Australia and Canada, whose guidance includes five stages with the inclusion of death and bereavement. Providing bereavement care to families is considered to be an integral part of care provision [18, 20]:

1. Disease advancement.
2. Experiencing life-limiting illness.
3. Dependency and symptom increase.
4. Decline and last days.
5. Death and bereavement.

Other organizations provide similar assessment tools to help healthcare professionals in determining if an individual is entering the end-of-life phase. The Supportive & Palliative Care Indicators Tool (SPICT™, University of Edinburgh, UK), developed in Scotland, provides this information for people from a variety of countries and in particular those from a low-income setting. These tools are available in different languages [21].

Management of diabetes at the end of life

The care of the dying person with diabetes is challenging, encompassing changes to glycaemic target ranges, determining individual and carer expectations, reducing the risk of hyperglycaemia and hypoglycaemia, managing the effects of other medications, such as glucocorticosteroids, and tailoring diabetes medications depending on the stage of end of life. Planning for end-of-life care in people with diabetes is often seen as a direct choice between treating or withdrawal of treatment for diabetes [11, 13, 20]; in practice, caring for the dying person is more complex, especially when they have diabetes.

Planning for the end of life (advance care planning) should start early so that the individual can clearly document their values, the things that give meaning and purpose to their life, and the care they

Box 73.1 Gold standards framework for end-of-life care

The 'surprise question': would you be surprised if this person were to die in the next few months, weeks, or days?
The answer to this question should encompass a range of clinical, comorbidity, social, and other factors that give a whole picture of deterioration. If the healthcare professional would not be surprised, then it is important to consider what measures might be taken to improve the person's quality of life now; and in preparation for possible further decline to check whether their advance care plan for end of life is still current.

General indicators of decline: deterioration, increasing need, or choice for no further active care
These include:
- Decreasing activity: functional performance status, declining limited self-care, in bed or chair 50% of day, and increasing dependence in most activities of daily living.
- Comorbidity, which is regarded as the biggest predictive indicator of mortality and morbidity.
- General physical decline and increasing need for support.
- Advanced disease with an unstable, deteriorating complex symptom burden.
- Decreasing response to treatments.
- Decreasing reversibility of exacerbations of underlying illnesses, which indicate reducing reserves.
- Individual chooses to have no further active treatment.
- Progressive weight loss (>10%) in past six months.
- Repeated unplanned or crisis admissions.
- Sentinel event, e.g. serious fall, bereavement, transfer to nursing home.
- Serum albumin <25 g/l.
- Considered eligible for additional financial support and benefits.

For people with diabetes who are using insulin or β-cell secretagogues, the development of hypoglycaemia should be added to the indicators that a person is at the end of life. It has long been recognized that the development of hypoglycaemia in people who have not previously been prone to this is a poor prognostic sign [17]. This is true for hospitalized individuals, in whom the excess mortality is not caused by hypoglycaemia *per se*, but by associated comorbidities [18]. It seems that this also applies to out-of-hospital hypoglycaemia. An audit of 1835 paramedic call-outs for hypoglycaemia in 2015 in the UK revealed that within one year following the call-out, 4.4% of people with type 1 diabetes and 22% of those with type 2 diabetes had died [19]. Hypoglycaemia in this context is multifactorial, arising from reduced food intake, weight loss, and/or impaired kidney function without adjustment of the dose of hypoglycaemic medication.

Factors related to the risk of hypoglycaemia include taking insulin preparations, sulfonylurea (e.g. gliclazide, glipizide, glimepiride), and prandial regulators (nateglinide, repaglinide). People with diabetes who are at particular high risk include those who also have one or more of the following:
- Poor appetite/erratic eating pattern.
- Weight loss.
- Renal deterioration.
- Liver impairment/carcinoma.
- Autonomic neuropathy (gastroparesis).
- Nausea and vomiting.
- Previous gastrectomy.
- Frailty.
- Memory problems.
- Oropharyngeal and oesophageal tumours [13].

Specific clinical indicators related to certain conditions
These relate to specific conditions, such as cardiovascular disease. Although diabetes is not mentioned, it frequently occurs in association with those conditions that are specifically mentioned, including cancer, chronic obstructive airways disease, heart disease, renal disease, general and specific neurological disease, such as motor neurone disease, Parkinson's disease, and multiple sclerosis, frailty, dementia, and stroke [1].

will accept or not accept in specific situations. Clearly documented values help healthcare professionals and families make decisions about the care the dying person would accept when the person no longer has decisional capacity, even if they have not documented the specific care they do or do not want [11, 13].

There was a dearth of guidance on end-of-life diabetes care until Dunning et al. first published their guidance in 2010 [22]. Most other generic end-of-life guidelines did not attempt to address the specific issues encountered by people with diabetes, so Diabetes UK commissioned a working party in 2010 to review available data and the existing guidance from around the world. The agreed aim of the working party was to summarize a consistent but high-quality approach towards end-of-life care for people with diabetes by providing guidance and clinical care recommendations. These

were developed in partnership with multiple professional groups and formed a consensus of opinion across care and professional boundaries [23]. The original Diabetes UK guidelines have been revised over the years. The latest update was commissioned by Diabetes UK and undertaken by Trend Diabetes in 2021. This included more specific updates relating to cancer, chronic kidney disease, and Covid-19 [13].

These and other guidelines formed the basis of the inclusion of sections on end-of-life care within clinical guidelines for managing type 2 diabetes, such as the International Diabetes Foundation's (IDF) Global Guideline for Managing Type 2 Diabetes [24] and the RACGP/Diabetes Australia guidelines for Managing Type 2 Diabetes [25].

The key principles underlying high-quality diabetes care at the end of life are summarized in Table 73.1. The consensus recommendations addressed the major clinical problems that people with diabetes encounter at the end of life and how these could best be managed. The recommendations were aligned to the generic Gold Standards Framework for end-of-life care [16]. They included a review of the use of anti-diabetes therapies and set glycaemic targets that aimed to minimize hypoglycaemia and improve safety for the individual. UK algorithms developed in 2013 for specific situations, such as use of daily steroid therapy and treating hypoglycaemia, have since been updated (Figure 73.1) [13]. It was hoped that these guidelines would contribute to the development of a consistent approach to care delivery and act as a platform for future partnerships among all healthcare sectors and the public.

Glycaemic targets

There have been no well-designed studies supporting or providing insight into glucose regulation, diabetes self-management, or the use of particular diabetes therapies at the end of life. Maintaining appropriate metabolic management at all terminal stages of life might seem an achievable goal in most people with diabetes, but the influences of the stress response to severe illness, disturbances in glucose metabolism caused by malignancy, use of steroids, and frequent infections can be challenging for clinicians providing diabetes care. People dying with diabetes may have an increased frequency of symptoms such as pain, constipation, and fatigue, which can be difficult to ameliorate unless healthcare professionals have experience providing tailored diabetes therapy in combination with adequate pain relief including use of opiates, when indicated for symptom control.

There is no evidence to justify the use of glycated haemoglobin (HbA_{1c}) testing in end-of-life diabetes care. The optimal range of blood glucose values will vary according to the stage of the illness, nutritional status, and diabetes treatments given [13, 24]. Others have argued that measuring HbA_{1c} should cease when estimated survival is only a few months, not least because using HbA_{1c} to diagnose diabetes in this situation is not validated [26].

It is likely that the optimal glycaemic range will vary according to the stage of illness, the ability to eat and drink normally, the risk of hypoglycaemia, the nutritional status, and concomitant treatments. Many people prefer not to have frequent blood glucose estimations, particularly if they understand that the result may not have an immediate impact on management; their wishes should be respected.

Some have argued for a blood glucose target range of 180–270 mg/dl (10–15 mmol/l) or even up to 360 mg/dl (20 mmol/l), although the latter may not be appropriate because of the increased risk of ketoacidosis in people with type 1 diabetes and hyperosmolar states in those with type 2 diabetes. Consensus guidance for glycaemic targets recommended 6–15 mmol/l (108–270 mg/dl) and this range is one of the suggested quality metrics for end-of-life care (Box 73.2) [2, 13, 22]. This range will help to avoid hypoglycaemia and hyperglycaemia in individuals in the last year of life. The number of daily capillary blood glucose tests should be reduced in those with type 2 diabetes in tandem with the reduction or cessation of diabetes medications as the individual enters the final months, weeks, and days of life. Individuals with type 1 diabetes will need to remain on insulin until death to avoid diabetic ketoacidosis. Blood glucose testing should continue in this situation at least on a daily basis to rule out overt hypoglycaemia or hyperglycaemia. The use of continual glucose monitoring systems can be useful tools in some cases, as this will be less invasive [13].

Since people with diabetes are increasingly used to a care planning approach in which they take informed decisions about their care, everyone with capacity should continue to be involved in their care planning for as long as possible, including decisions about setting blood glucose and other target ranges and the frequency of blood glucose monitoring [11, 13]. Ideally, documentation of an end-of-life advanced care plan should be in place as early as possible to help avoid uncertainty for healthcare professionals and families.

Medicines management during the last year of life

Specific recommendations that are aligned to life expectancy are given in the IDF and UK guidelines. In general, non-insulin glucose-lowering therapies can be reduced and eventually stopped depending on other factors, such as poor appetite, weight loss, and anorexia (Table 73.2). It may be necessary to discontinue insulin treatment in people with type 2 diabetes, but insulin should never be stopped in people with type 1 diabetes (Table 73.3). However, managing blood glucose levels to avoid hyperglycaemia and hypoglycaemia is essential to control the unpleasant symptoms associated with these conditions. Thus, insulin can be used with a palliative intent.

Other non-diabetes medications

Once it is recognized that a person has reached the end of their life, a review of all prescribed medication is indicated. It is important to stop or reconsider doses of any medicines that are not beneficial and those that are causing symptoms. Many people with diabetes are prescribed medication intended to reduce the risk of cardiovascular events in the long term, including angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists, other antihypertensives, aspirin or anti-platelet agents, statins, and other lipid-lowering agents. There are significant potential side effects associated with these medicines and stopping some or all of them may improve quality of life.

Decisions should be made in conjunction with the individual and their family, to avoid giving the impression that their medical advisers are 'giving up on them'. Most decisions to reduce or stop medicines are usually based on clinical common sense rather than robust evidence. A proactive approach to de-intensifying therapies should be based on the risk–benefit impact of continuing them. Any changes need to be made in agreement with the individual and/or their family [13, 14]. Drugs frequently used in palliative care include antisecretory drugs, analgesics, and sedatives and relaxants. Experts in the field of palliative care should advise on the use of these drugs [13].

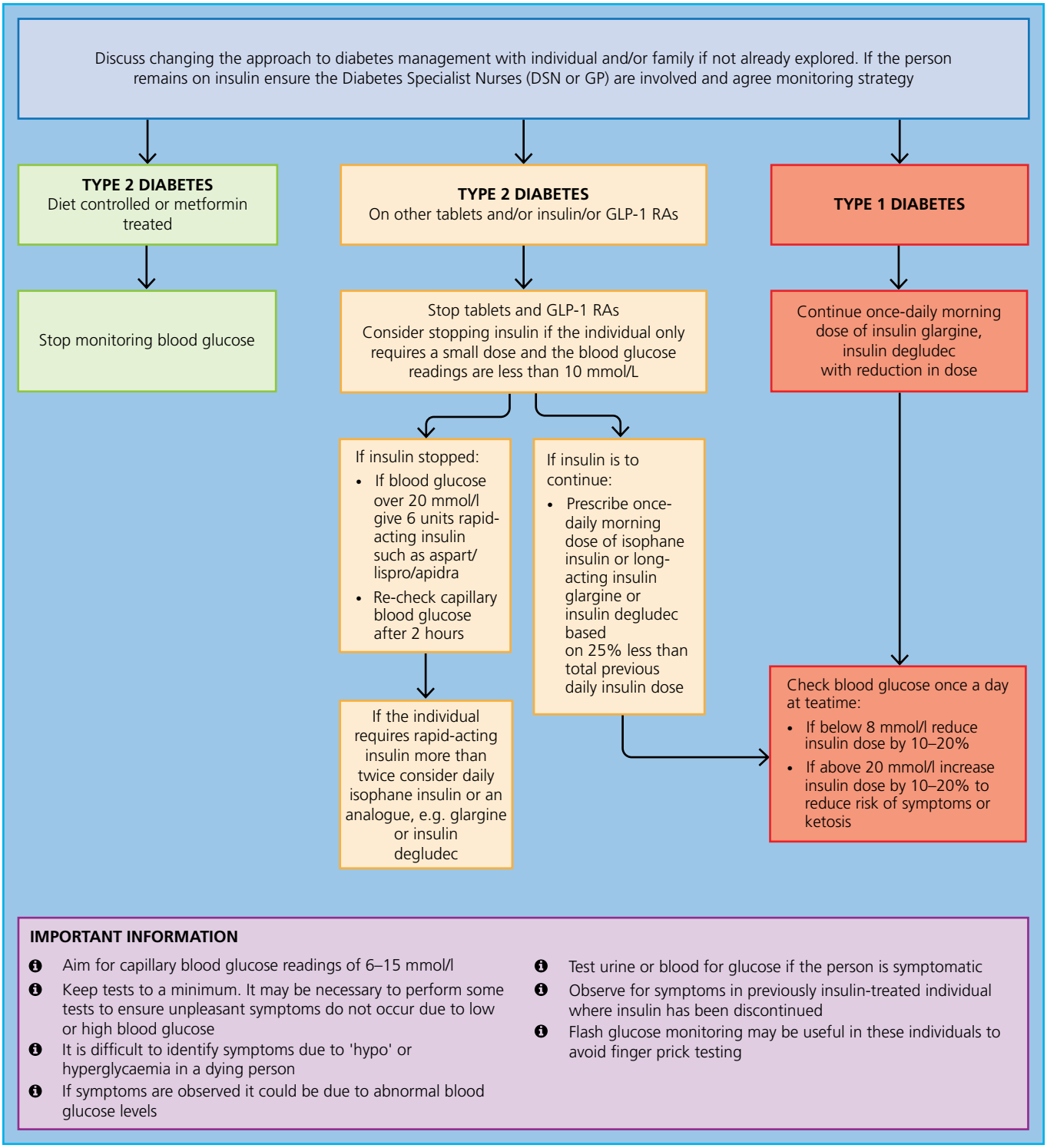

Figure 73.1 Management of diabetes in the dying person. GLP-1 RA, glucagon-like peptide 1 receptor agonist.

Box 73.2 Glucose targets for end-of-life care

Aim 1: No glucose level less than 6 mmol/l (110 mg/dl).
Aim 2: No glucose level higher than 15 mmol/l (270 mg/dl).

The UK algorithm for diabetes at the end of life (Figure 73.1) provides guidance on how to manage diabetes in the dying person. It can be reassuring for relatives and carers to know that these recommendations for end-of-life care are being followed and that diabetes is being *managed differently* rather than being *ignored*. The

Table 73.2 End-of-life medicine management: non-insulin therapies.

Metformin standard or Metformin SR	Sulfonylureas Gliclazide, glipizide, glimepiride, repaglinide	Pioglitazone	Gliptins Alogliptin, linagliptin, saxagliptin, sitagliptin	GLP-1 RAs Exenatide or liraglutide, lixisenatide, semaglutide, exenatide extended release, oral semaglutide, dulaglutide	SGLT-2 inhibitors Dapagliflozin, empagliflozin, ertugliflozin, canagliflozin
Risk of hypoglycaemia with non-insulin therapies when used as mono-therapy					
✖ No risk	✓ Moderate risk	✖ No risk	✓ Low risk	✖ No risk	✓ Low risk
General considerations					
Review dose according to changing renal function	Review if dietary intake is reduced and/or there is significant weight loss	The risk–benefit ratio for pioglitazone in individuals with terminal disease requires review and should only be prescribed if benefits can clearly be identified	Review doses in accordance with individual licences if renal function deteriorates	Review if eating patterns change or significant weight loss occurs	Refer to SPC for doses
Withdraw if creatinine >150 mmol/l or eGFR <30 ml/l/1.73 m^2	Review dose if renal or liver function deteriorates and consider a switch to tolbutamide		Some gliptins can be used for all stages of renal disease	Withdraw if abdominal pain or pancreatitis develops	Refer to individual SPC for renal guidance
Review if gastrointestinal disease is present or symptoms of nausea, heartburn, diarrhoea, or flatulence are making individuals miserable with discomfort	Review tolbutamide dose if liver function deteriorates as hypoglycaemia may occur	Should not be used in individuals with or at risk of bladder tumour or heart failure	Combination with sulfonylurea increases the risk of hypoglycaemia	Refer to individual product SPC for doses	Stop if evidence of clinical dehydration, peripheral vascular disease, or foot ulceration in acute illness and pre-surgery Test for ketones if there is acute illness

eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SGLT-2, sodium–glucose cotransporter 2; SPC, summary of product characteristics.Source: Modified from James et al. 2021 [13]. Reproduced by permission.

Table 73.3 End-of-life medicine management: insulin therapies.

The simplest regimen should be chosen if switching to insulin only. Both once- or twice-daily injection can be considered
Doses may need to change with changes in renal function
Equipment for insulin delivery may need to be reassessed if physical capabilities alter, manual dexterity or vision is poor, or carers become involved in administering insulin
Carers and healthcare professionals may need education to safely manage insulin
Hypoglycaemia risk will need to be reassessed when eating patterns change
An evening basal insulin in combination with daytime oral anti-diabetes agents may be a good first-line treatment choice
A change of insulin regimen may be needed to match changes in food intake and activity levels

flowchart was designed to minimize symptoms of diabetes and keep invasive testing to a minimum.

Insulin

The general principles of insulin management are summarized in Table 73.3. Insulin therapy should not be completely withdrawn in type 1 diabetes due to the risk of diabetic ketoacidosis. Insulin requirements in the last months and weeks of life in people with type 2 diabetes, however, often significantly reduce as appetite diminishes, and insulin can be reduced or even discontinued in some individuals.

Continuous subcutaneous infusion of insulin–insulin pumps

Insulin pumps are increasingly being used to manage diabetes in an end-of-life phase; there is limited value in the extensive training of healthcare professionals in their use, however, as insulin pump users are likely to be well informed about adapting their pump settings for illness and have a good awareness of food intake in terms of carbohydrate and protein content. If the person with diabetes feels capable of using the pump, they should be encouraged to do so; nevertheless, carers may need education in pump use and insulin dose adjustment if it is physically difficult for the person with diabetes to make setting and cannula changes. Members of the specialist team who are adept at dealing with lifestyle and appetite changes in managing pumps may need to develop their understanding of the implications of chemotherapy or radiotherapy regimens in order to give appropriate advice.

Should the individual wish to continue to use their insulin pump, the infusion rates can be adapted to cope with even the last days of life. Close cooperation between diabetes specialist teams is crucial, since the caring team may be unfamiliar with the insulin

pump. The diabetes specialist team can advise about alternative insulin regimens in situations where pump treatment is no longer considered to be appropriate or feasible, but planning ahead will minimize the understandable anxiety associated with switching to a different insulin delivery method. This could and should be documented in the individual's advance care plan. On a practical note, insulin pumps may be returned to the issuing department when they are no longer required, as they can be reconditioned and reissued.

Nutrition

It is important that people in end-of-life care are reviewed regularly to determine whether they are becoming malnourished or dehydrated. If there are concerns that an individual is not receiving adequate nutrition or hydration by mouth, even with support, an assessment of their condition and their individual requirements must be undertaken and consideration given to different forms of clinically assisted nutrition consistent with their advance care plan. If the individual refuses to eat or drink or has swallowing difficulties, an assessment of the underlying cause, for example depression, dry mouth, oral candidiasis, or painful mouth ulcers, and possible treatment should be offered [9, 13, 27, 28].

Individuals treated with chemotherapy may experience loss of taste and this treatment can induce nausea and vomiting. Eating helps people to feel better and is a social activity. It is a great concern to individuals and their families when there is loss of appetite and weight, and an inability to participate in the family eating together. Food supplements, although glucose rich, are sometimes the only nutrition that is tolerated. If these are used, a treatment review should be undertaken to avoid symptoms of hyperglycaemia [9, 13, 28, 29].

Poor appetite or reductions in meal size along with swallowing difficulties experienced by some individuals will affect glycaemic levels and may lead to hypoglycaemia. People with type 2 diabetes may be taking several oral anti-diabetes therapies, which may be difficult to swallow because of tablet size or the number of medications prescribed. In these instances, a medication review should be undertaken and treatment regimens simplified. Individuals may also prefer to take smaller meals more frequently. Avoidance of glucose-rich foods may no longer be appropriate; consequently, diabetes therapies may need to be adjusted to reduce hyperglycaemic symptoms. It is entirely appropriate to relax dietary restrictions originally designed to minimize weight gain and stabilize glucose levels. People with diabetes can be offered any of their favourite foods in order to tempt them to eat. Other guidance includes:

- Consider using metformin in powdered form or syrup (if it is available) if people cannot cope with tablets.
- Avoid sulfonylurea preparations to reduce hypoglycaemia risk.
- If small meals are being taken, repaglinide can be useful for managing small regular meals, with dose adjustments according to food intake.
- Low-dose insulin may be the only option for people whose glucose levels are high despite a significantly reduced oral intake.
- People with poor intake will need lower doses of insulin to avoid hypoglycaemia.

In some cases individuals may be on enteral feeding to provide adequate nutrition and to avoid hypoglycaemia and hyperglycaemia and unpleasant symptoms. A referral should be considered to the dietetic services, who may assist with a nutritional assessment and meal planning [11, 13].

Managing diabetes in people treated with glucocorticosteroids

The use of steroid therapy in people at the end of life can alleviate symptoms, reduce fatigue, increase appetite, and improve quality of life [30]. Steroids can be given using various regimens and in variable doses. The most common method is a short course of prednisolone given in the morning, which will lead to raised blood glucose readings later in the day that reduce overnight.

Individuals living with cancer are often treated with dexamethasone twice daily, which can lead to hyperglycaemia throughout the 24-hour period. The use of dexamethasone in individuals with Covid-19 has also become a staple part of their treatment plan (Figure 73.2) [30].

The commonest treatment for steroid-induced hyperglycaemia is a sulfonylurea, such as gliclazide, or isophane (neutral protamine Hagedorn, NPH) insulin (Table 73.4) [13]. People taking very short courses of steroids (<3 days) may only require close monitoring. Target ranges should aim to achieve a blood glucose concentration between 6 and 15 mmol/l (108–270 mg/dl) and no osmotic symptoms. Any diabetes treatments should be reduced or stopped in tandem with steroid reduction to avoid hypoglycaemia.

Withdrawing diabetes and other medication

The decision to withdraw treatment including anti-diabetes medication is difficult. Recognizing the concept of a good death for all people entering an end-of-life phase can be an awkward aspect of caring to communicate. Key priorities should be decided with the individual and their family as early as possible and documented in an advance care plan. Generally, people want to be free from pain, to be with family and loved ones, and to be treated with dignity and respect at all times [31].

The use of an advance care plan or a living will is becoming more common. An advance care plan is a legal document in many countries; it needs to be signed and witnessed and enables the person with diabetes to accept or refuse specific types of treatment at an indeterminate time in the future. Healthcare professionals need to know if an advance care directive or plan is in place [13, 31–34]. Most guidance recognizes that any withdrawal of diabetes-related treatments warrants close liaison with the person with diabetes, the family, and the family doctor, and *must* consider the person's wishes, family concerns, and the presence of an advance directive.

Treatment withdrawal can be considered:

- When the person with diabetes is entering the terminal phase of life.
- Where frequent treatment-related hypoglycaemia is causing distress and significant management difficulties.
- Where continued treatment with insulin poses an unacceptable risk of hypoglycaemia or where the benefits of stricter glucose management cannot be justified.
- Where continued use of blood pressure or lipid-lowering therapy cannot be justified on health benefit considerations.

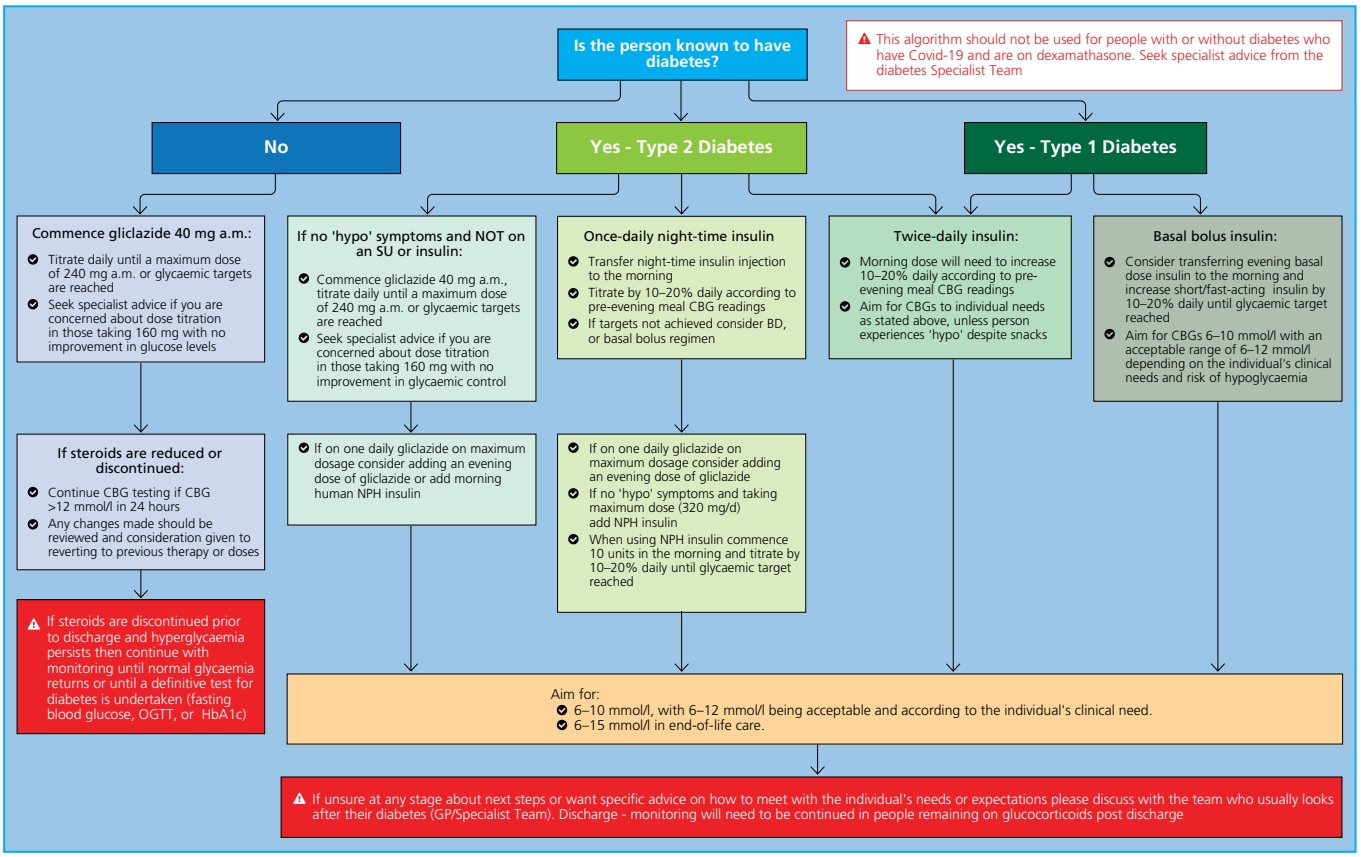

Figure 73.2 Algorithm for managing glucose with once daily steroid therapy. BD, twice daily; CBG, capillary blood glucose; HbA_{1c}, glycated haemoglobin; NPH, neutral protamine Hagedorn; SU, sulfonylurea.

Table 73.4 Suggested treatments for hyperglycaemia when using steroids.

Regimen	Treatment
Once-daily steroid therapy	Morning administration of a sulfonylurea, e.g. gliclazide, or morning isophane NPH insulin
Twice-daily steroid therapy	Consider using a twice-daily sulfonylurea (e.g. gliclazide) or isophane insulin If hypoglycaemia is a concern, consider changing to a long-acting insulin analogue, such as insulin glargine or insulin degludec

Source: Joint British Diabetes Societies for Inpatient Care 2021 [29].

- Where continued food or fluid is not the choice of the individual who is dying.
- Where prescribing anti-infective therapy is unlikely to benefit the individual.

Workforce

Dissatisfaction with and complaints about care provided at the end of life still occur too frequently and are usually attributable to inadequate understanding of the complexities of the situation, failure of communication, or both. Lack of workforce knowledge and training to deliver end-of-life care is a common feature of professionals delivering diabetes care in both hospital and community settings [14, 35].

Conversely, palliative care clinicians may lack up-to-date skills in diabetes medication and management, which affects their ability to offer holistic packages of care. Healthcare professionals need to know where their area of responsibility lies and recognize when they need to consult with other team members and colleagues, specialist teams, social services, or voluntary organizations in order to ensure a holistic approach to care. All staff caring for individuals at the end of life should receive initial and ongoing training and have been assessed for competency [35, 36].

Competency is defined as 'The state of having the knowledge, judgment, skills, energy, experience, and motivation required to respond adequately to the demands of one's professional responsibilities' [22]. The competency framework from the comprehensive Integrated Career and Competency Framework for Diabetes Nursing illustrates the different competencies expected of healthcare professionals and unregistered practitioners involved in the care of someone with diabetes at the end of their life [35].

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12 Delivery and Organization of Diabetes Care

74 The Role of the Multidisciplinary Team across Primary and Secondary Care

Samuel Seidu and Kamlesh Khunti
Diabetes Research Centre, University of Leicester, Leicester General Hospital, Leicester, UK

Key points

- The rising prevalence of diabetes coupled with increasing life expectancy makes it impossible for specialist centres to cope with the demands of diabetes care, thus necessitating a shift to primary care.
- In an integrated diabetes care model, innovative collaboration between primary care and specialists can result in the creation of new healthcare organizations that can provide integrated diabetes care for their local populations.
- Care provision in community settings (i.e. other than within general practices) requires a collaborative unit of diabetes specialist support teams based on the needs of the local population.
- Multidisciplinary teams are essential for the care of people with diabetes from early life to end of life.
- Multidisciplinary teams are essential for the management of various complications of diabetes.
- The composition of multidisciplinary teams should span a wide range of specialties and community care workers in order to address the complexities of diabetes.

Diabetes has been recognized as a global epidemic. In 2019 the prevalence of diabetes was estimated to be 463 million worldwide and this is expected to rise to 700 million by 2045 [1]. It is a complex chronic disease affecting multiple organ systems, often accompanied by other comorbid conditions, with an associated disease management burden for the individual with the condition. The rising prevalence coupled with the increasing life expectancy makes it impossible for specialist centres to cope with the demands of diabetes care, as they did until ~30 years ago, thus necessitating a shift to primary care (Box 74.1) [2]. Community or primary care diabetes management is therefore a logical focal point for implementing strategies that improve the care of individuals with diabetes [3]. Multifactorial intervention in the management of type 2 diabetes leads to reductions in cardiovascular mortality [4, 5]. The management of the multiple cardiovascular risk factors in diabetes care requires multidisciplinary teams. The organization of these teams needs clinicians not just to have expertise in their chosen fields, but to be skilled in an interprofessional approach. The multidisciplinary approach to diabetes management is based on the premise that against the background of a common framework, decisions on the aims of treatment should be dictated by the insight of several professions. This normally requires team building, which focuses on developing a common culture and giving priority to professional and social interactions. The purpose of this multidisciplinary

Box 74.1 Definitions

- *Cardiovascular* refers to risks and complications related to the heart and the vessels.
- *Care* refers to the provision of what is necessary for the health of people with diabetes.
- *Community* refers to the care of individuals with diabetes outside of the hospital setting, usually delivered by specialists.
- *Diabetes* refers to all types of diabetes.
- *Integration* refers to bringing together people of different healthcare professional backgrounds into unrestricted association, with the aim of delivering a seamless care package for people with diabetes.
- *Models* refer to a system of care worthy of emulation.
- *Multidisciplinary* refers to the combination of various healthcare disciplines to care for individuals with diabetes.
- *Primary* refers to care of people with diabetes by general practitioners or family physicians.
- *Specialist* refers to physicians with special interest in diabetes. These are usually based in the hospital setting.
- *Team* refers to the coming together of health professionals to achieve a common goal.

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approach is to ensure that activities around the complexities of screening, diagnosis, early and late management, and treatment of complications are coordinated in a seamless, integrated approach, with the aim of ensuring an optimal individualized management plan for each person with diabetes.

Coronary heart disease is a frequent complication and a major cause of mortality in people with diabetes. Therefore, its presence can create added complexity for an already burdensome regimen. People with type 2 diabetes also experience further burden from other, non-cardiovascular comorbidities (e.g. osteoarthritis, chronic obstructive pulmonary disease), with only 17.6% having only diabetes [6]. Those >65 years old will have a median of 6.5 other conditions in addition to diabetes, whereas those <65 will have a median of 2.9 other conditions [6]. The treatment of the complications and comorbidities requires coordination across several specialists. System management is therefore essential, including the flexibility to deliver personalized care and identify and meet the individual requirements of people with complex needs. In dealing with these complexities, integration of care around the individual with diabetes is pivotal to deliver seamless, optimal, and effective care. Integration refers to bringing together people of different healthcare professional backgrounds into unrestricted association, with the aim of delivering a seamless care package for people with diabetes.

The process is enhanced by telemedicine, which promotes self-monitoring of the individual with diabetes and enables the provision of accurate and timely data transmission and sharing between people with diabetes and clinicians. It fosters innovative approaches to streamlining diabetes management and monitoring. There is now an opportunity for virtual clinics, run jointly by generalists and specialists joining in at the same time [7].

Upskilling of primary or community care professionals in multidisciplinary teams

In an integrated diabetes care model, innovative collaboration between primary care and specialists can result in the creation of new healthcare organizations that can provide integrated diabetes care for their local populations. With the person with diabetes at the centre, delivery of care can revolve around them, with the aspiration of having an organizational structure, clinical pathways, and financial planning all aligning seamlessly [8]. The subsequent care pathway developed should be customized to the wide-ranging needs of the local population and adapted to the evolving needs and changing national health agendas, instead of a *one-size-fits-all* model. The prime focus of the integrated diabetes service is the integration of the healthcare system and the coordination of services around a person with diabetes, bringing together primary and specialist care in a setting nearer the person's home, where applicable.

To successfully maintain or even improve clinical outcomes and reduce variation in care, while supporting this shift of care, upskilling of general practitioners, practice nurses, and healthcare assistants and ongoing support from specialists are required. This comprehensive healthcare professional upskilling process needs to be based on psychological theories of learning [9–11] with the necessary knowledge repertoire. This will hopefully equip the diabetes care workforce with the appropriate knowledge and skills to provide them with the confidence to deliver the highest-quality care and improve outcomes for the individual with diabetes.

Possible areas of training could include mentorship and case management at a practice level to support clinical development, training, and care planning. Not only should the education and training be available at differing levels, they need to be provided by multiple alternative and complementary methods, including workplace-based leaning, distance learning, a modular format, journal clubs, and mentorship [12]. The multidisciplinary team creates an adaptable and responsive model with a feedback mechanism, which encourages improvement of the quality of care through knowledge of local needs. Furthermore, and crucial for such an educational programme's longevity, it must be developed so that it can reflect continually changing approaches to diabetes management in relation to new therapies and national drivers [12].

Practices that participate and engage in this training process can gain accreditations based on the breadth and level of diabetes care that they provide [12]. A stepwise and ongoing accreditation process could start from the provision of a basic core service, including screening of all individuals at risk of diabetes, diabetes-prevention interventions, regular surveillance of all people with diabetes (i.e. measuring and managing glycated haemoglobin [HbA_{1c}] according to guidance, blood pressure and cholesterol measurements, and feet examinations), cardiovascular disease risk reduction, evidence-based prescribing, auditing care provided, and evidence of referral to and attendance of all people with diabetes at evidence-based educational interventions/programmes directed to the person with diabetes [12].

A step up the accreditation ladder will be practices that provide elements of an enhanced service, including the management of complex treatment conditions around the person with diabetes on insulin, including in-house initiation and titration for those with type 2 diabetes, management of people with stable type 1 diabetes, initiation and management of glucagon like-peptide 1 (GLP-1) receptor agonist therapies, high-quality care for housebound individuals (including those in nursing/residential homes), and proactive discharge of individuals who may benefit from the treatment and are currently under specialist follow-up [12].

Multidisciplinary team support in structured diabetes self-management education

People with diabetes must live the rest of their lives with the condition and as such need to improve their knowledge, skills, and confidence, enabling them to take better care of their own condition. They must integrate effective self-management into their daily activities. These can be achieved through structured education programmes [13].

The multidisciplinary team will need to consider a range of issues to ensure that their education programmes meet the expected standards. The programme must have a written curriculum, and include areas such as healthcare professional training, quality assurance, and learning needs assessment [14]. Healthcare professional training should incorporate modules around person-centredness. Professional training in cultural diversity awareness in diabetes, self-management initiatives including motivational interviewing and other behaviour change interventions, and psychosocial aspects of diabetes will help multiprofessional teams develop working plans to achieve the desired goals [13].

This structured training for diabetes educators must address the theoretical base and the underlying philosophy of structured diabetes education. The programme itself must therefore be

underpinned by the philosophy that the programme will be adaptable to the needs of the person with diabetes and involve them in its ongoing development. It should be evidence based and have a clear aim and learning objectives, which are shared with the individuals with diabetes, carers, and family. Health professionals must plan *with* the individual with diabetes on issues around the care of their condition.

Local multidisciplinary teams have the responsibility of ensuring that there is an internal quality assurance process in place for the structured education programmes. This ensures that practitioners are carrying out self-reflection during the delivery of the programme with ongoing review of the biometric outcomes, user satisfaction, and experience in order to maintain standards [15].

Like in other chronic diseases, the use of digital health interventions is increasingly becoming integrated into diabetes self-management to improve accessibility for individuals with diabetes, enhance behaviour change, and improve glycaemic management [16, 17]. With people with diabetes able to access web-based programmes at the own time and pace, the problems associated with face-to-face structured education programmes, such as time and transport, can be better addressed with digital interventions [18].

Multidisciplinary teams in diabetes care models

In developing a diabetes service, it is important to know what the components of the service need to be and the mode of implementation required. Even though the models of care delivery in diabetes vary from country to country, the components are broadly similar. The implementation is what varies from place to place. The choice of implementation strategy depends on the local needs and the availability of various component resources. In most high-income countries, there is usually a national strategy for delivering diabetes care.

In a generic service model, there must be integration across all levels of the service to provide a seamless transition for individuals with diabetes and ensure that appropriate referrals take place, with clear and agreed referral criteria and clinical protocols for chronic and emergency management (Figures 74.1 and 74.2). Good communication links and joint working between the practice diabetes leads and specialist care teams are essential to plan services and to provide a framework for audit, quality assurance, and performance monitoring.

Care provision in community settings (i.e. other than within family doctor practices) requires a collaborative unit of diabetes specialists support teams. These teams are constructed based on the needs of the local population and can comprise a collaborative team of diabetes specialist nurses, diabetes consultants, dieticians, diabetic retinopathy screening teams, and podiatrists. They can offer clinic-based care, outreach support to primary care practices and nursing homes, rapid-access community clinics, development of agreed clinical care pathways for various aspects of diabetes care and referrals, and telephone- and web-based support for complex cases, again depending on the needs of the locality. This support has to be flexible in approach and multistranded to reflect the varying gaps in knowledge of the healthcare professionals. The fundamentals of any such programme should be applicable and transferable to other diabetes care providers.

These components require a coordinated approach between multiple healthcare professionals in different sectors of health and social care. For local populations a local model of care is required, which can be developed in more detail, with roles and responsibilities clearly identified. Ideally, care should be provided within each locality to agreed care pathways, and each care provider should be clear of their role and relationship with other providers. The delivery of integrated diabetes care in any locality requires leadership and teams working through cooperation, coordination, and collaboration, working to a shared vision of healthcare, and drawing together skills and relationships across the healthcare community. This integrated, collaborative approach is effective not only in mental illness, but also in the management of people with mental disease and other chronic physical multimorbidities, including diabetes [19]. Specialist diabetes teams, often with extended roles,

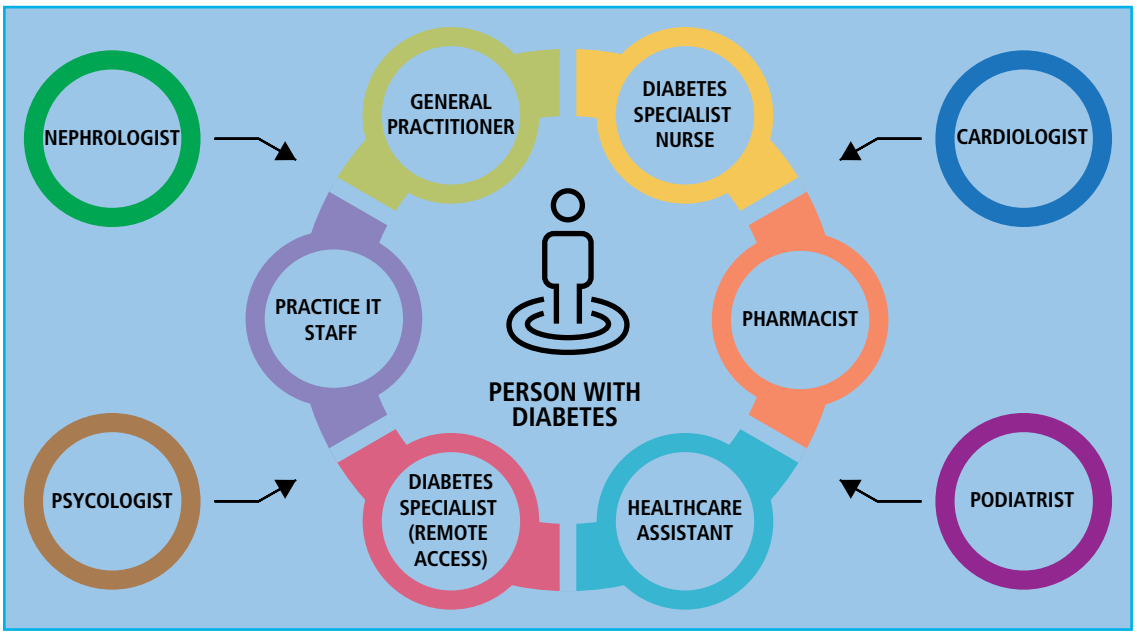

Figure 74.1 Schematic representation of the management of people with multiple long-term conditions in countries with advance health systems. In areas where resources abound, multidisciplinary primary care teams, supported by specialists, provide holistic care to the person with diabetes. IT, information technology.

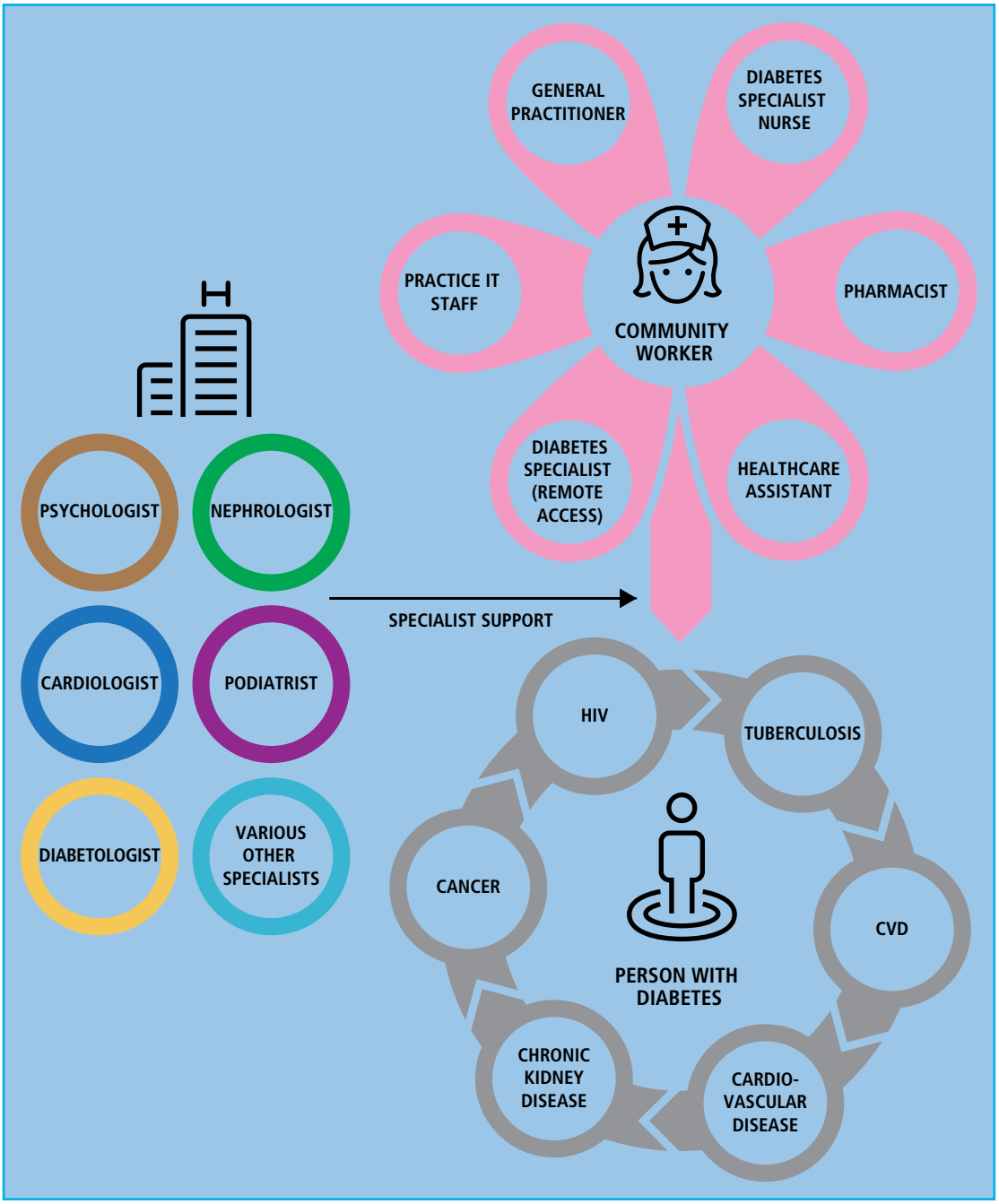

Figure 74.2 Schematic representation of the management of people with multiple long-term conditions in low- and middle-income countries. In the context of multimorbidity and limited human and financial resources, non-specialized nursing and allied health professionals, supported by specialists, provide holistic care to patients. CVD, cardiovascular disease; HIV, human immunodeficiency virus; IT, information technology.

working in primary care through community consultants, form a central *hub* of expertise to support the delivery of high-quality and effective diabetes care (Figure 74.1).

In the USA, there is a drive to incorporate elements of the chronic care model into diabetes care. Systems' redesigns, self-management and decision support, and organization of diabetes care in the community could collectively improve outcomes in diabetes and reduce cost [20]. Organizations like Kaiser Permanente are using these components in diabetes care and showing improvements in admission rates and outpatient clinic attendances [21].

The situation is much more challenging in low- and middle-income countries like sub-Saharan Africa, where diabetes care, largely driven by specialist care, faces competition for resources from the management of infectious diseases (Chapter 75). The lack of financial, infrastructural, and human resources is a major drawback for any effective service implementation in diabetes care, thus leading to lower life expectancy in people with diabetes [22]. Care provision is done using non-specialised nursing and allied healthcare professionals in the management of all chronic diseases including diabetes, without disease-focused specialization. In the context

of multimorbidity and limited human and financial resources, this approach seems to be an attractive option worth implementing and evaluating in other areas (Figure 74.2).

Multidisciplinary teams in the management of complexities in cardiovascular risk prevention

The presence of a complex health and illness profile is associated with worse management of cardio-metabolic risk factors independent of regimen intensity and history of cardiovascular disease (Chapter 46) [23]. The medical model of care is structured along system-based specialization, thus necessitating evidence-based guidelines for various conditions to be developed independently [24]. This creates a huge challenge for primary care teams, who must deal with various disease areas without thorough specialization. That is compounded by the fact that management of the major cardiovascular risk factors in diabetes has sometimes raised questions about the benefits of high-risk factor control. In glycaemic management, for example, although early intensive treatment in diabetes results in lasting benefit, including for cardiovascular risk reduction [25], intensive glycaemic management in late diagnosis and in individuals with background cardiovascular disease does not reduce major cardiovascular events and indeed may increase mortality [26]. Similarly, even though major reductions in cardiovascular outcomes are seen in individuals receiving tight control of blood pressure compared with those receiving conventional control if the baseline blood pressure was high [27, 28], tight control of systolic blood pressure among people with diabetes and coronary artery disease does not improve cardiovascular outcomes [29]. Indeed, increased mortality in intensively treated individuals with newly diagnosed diabetes has also been noted and therefore caution in lowering blood pressure too aggressively is recommended in these individuals [30]. Regarding cholesterol, a reduction in 1 mmol/l low-density lipoprotein (LDL) cholesterol leads to a 20–25% reduction in cardiovascular events (major coronary events, coronary revascularization, and ischaemic stroke) [31]. However, among individuals at increased diabetes risk (those with baseline evidence of impaired fasting glucose, metabolic syndrome, severe obesity, and elevated HbA_{1c}), the risk of development of diabetes among statin-treated individuals appears to be raised. However, the overall cardiovascular and mortality benefits of statin therapy exceed the risk for developing diabetes [32]. Nevertheless, this finding introduces another complexity in cardiovascular risk management in people with diabetes. Thus, the management of the various risk factors could potentially require input from other team members with expertise in these areas.

The increasing prevalence of comorbid cardio-renal conditions coupled with the emergence of therapeutic agents that provide cardio- and nephro-protective benefits also calls for integrated, team-based care for the optimal treatment of these individuals with a complex condition. Local information technology (IT) infrastructure enabling shared records between primary care, nephrologists, cardiologists, and diabetologists is required, as well as providing secure data centres to facilitate monitoring of clinical outcomes and service improvement. This can assist people with diabetes, carers, and healthcare professionals with the choice of therapeutic options, understanding of the disease and its complications, and self-management [33]. Using integrated IT systems, provision of therapies and services to people with diabetes in different healthcare settings is made possible by ensuring responsiveness to the needs and preferences of the individual, improvements in healthcare process and intermediate outcomes, user–clinician communication, and access to medical information [34]. Due consideration, however, needs to be given to potential barriers in access to the IT infrastructure due to older age, low income, education, and cognitive impairment and to consider physicians' concerns about increasing their workload.

The presence of chronic kidney disease increases the risk of cardiovascular morbidity and mortality and increases the risk of progression to end-stage renal failure [35, 36]. Diabetic nephropathy is a progressive disease and as such requires the input of several healthcare professionals at various stages of the disease trajectory. The primary care teams after initial diagnosis of early disease can reduce the progression of renal disease with the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) [37, 38] and sodium–glucose cotransporter 2 (SGLT-2) inhibitors [39, 40].

Additionally, in heart failure, despite the improvements in treatment options, about half of people with the condition die within five years of diagnosis [41]. This and type 2 diabetes are major pandemics of the twenty-first century [42]. The introduction to routine clinical practice of SGLT-2 inhibitors with proven benefits in type 2 diabetes, heart failure [43], and chronic kidney disease [39, 40] will address the residual risk of a worsening of these cardio-reno-metabolic conditions over the coming years.

Specialist assessment should be available to individuals with diabetes with, or at high risk of, renal disease and heart failure for referrals by the primary care teams as the disease progresses. The late management and treatment of complications should be well coordinated between the diabetes and cardio-renal services. Diabetes, nephrology, and heart failure services should have appropriately trained staff and systems in place not just to organize the service effectively in a timely manner during disease deterioration, but to manage acute complications like hypoglycaemia during episodes of dialysis and end-stage heart failure. Multicomponent structured educational intervention programmes are effective in pre-dialysis and dialysis care [44]. The role of the dietician is invaluable in this group of individuals not only to maintain adequate nutrition, but to prevent abnormal electrolyte excursions [45].

Multidisciplinary teams in the care of people with diabetic retinopathy

The implementation of a retinopathy service should comprise a multidisciplinary team of clinicians who understand the natural history of the condition and options for early detection and treatment (Chapter 43). These will normally be permanent staff at a fixed or mobile retinal screening unit who are engaged in regular professional development updates. The aims of the service should be to improve access to retinopathy screening, particularly for those for whom access has traditionally been limited: the housebound, individuals who are disabled, older, Indigenous, or who do not speak the country's language. In the paediatric and adolescent populations, it is essential to have an ophthalmologist with expertise in diabetic retinopathy, and an understanding of the risk of retinopathy in the paediatric population, backed up by a team that has an experience in counselling young people and their families on the importance of early prevention and intervention [46]. The coordination and

supervision of such a service require proper leadership to identify clinical incidents, safety assessments, and drawing up proper interventions to tackle these deficiencies. The general practitioner keeps an updated register of people with diabetes for a call–recall system for retinopathy screening. This is coordinated through appropriate liaison between the hospital eye service and screening programme.

Successful multidisciplinary coordinated retinal screening services should have the necessary components not just for screening, but for investigation and management. There has to be immediate access to facilities for fluorescein angiography and optical coherence tomography to allow individuals with diabetic maculopathy to be treated within 10 weeks [47] and those with new proliferative retinopathy to be treated with laser within two weeks [48–50]. Individuals needing urgent photocoagulation should be able to have it carried out immediately. For the convenience of the individual, it is essential to have laser treatment carried out on the day of diagnosis, therefore there should be sufficient laser clinics or staff available to undertake the treatment outside laser clinics. Intravitreal drug delivery facilities will be needed at any treatment centre [49], but vitreo-retinal surgery, if not available locally, may require referral to a tertiary referral centre. For individuals with visual impairment, appropriate counselling services should be available.

Multidisciplinary teams in the care of people with diabetes-related foot ulcers

Many people with acute diabetes-related foot ulcers also have other multimorbidities including macrovascular complications and as a result healthcare professionals need to be mindful of these [51]. Foot ulceration has been reported as the leading cause of hospital admission and amputation in people with diabetes (Chapter 53) [52]. Acute diabetes-related foot ulcers require multidisciplinary management and best-practice care, including debridement, offloading, dressing, management of infection, modified footwear, and management of extrinsic factors [53]. Treatment of diabetes-related foot ulcers varies widely, depending on the skills of the attending clinicians. Best practice is deemed to be a multidisciplinary approach, where a holistic view of the individual with the ulcer is sought, and a care plan developed around this person's individual needs. However, these multidisciplinary teams are not always available. The multidisciplinary teams should ideally include appropriately trained staff such as orthoptists, podiatrists or podiatric surgeons or both, vascular surgeons, orthopaedic surgeons, diabetologists, microbiologists, radiologists, diabetes specialist nurses (including a diabetes specialist inpatient nurse), ward link nurses, and consultants in pain management with an interest in diabetic neuropathy [53].

For individuals at no added risk, foot care education is usually all that is required, but as they become at risk, twice-yearly review including foot inspection, footwear assessment, and foot care education become necessary. Individuals at high risk (i.e. those with more than two risk factors) need reviewing every 3–6 months, and may need vascular assessment or referral. Referral to a multidisciplinary foot care team within 24 hours for the management of ulcers and infection is mandatory [54]. To ensure a seamless package of care for people with foot problems, it is important that they are put at the centre of the decision-making process and have access to accurate information and support. The organization of care has to involve appropriate healthcare professionals, including community podiatrists, who have a clear referral pathway to specialist services. Multidisciplinary specialist teams must endeavour to hold joint clinics in order for the service to be more effective and to reduce duplication of visits [55]. For people in hospital with diabetes, close observation for risk factors and prevention of foot ulceration is crucial, as this can be a vulnerable situation with an increase in pressure-related ulcers.

For the seamless organization of care around the person with a severe diabetes foot condition, there needs to be a ready availability of services to support its management. Facilities for pressure area offloading include orthotic services, foot casting, and prosthetic services. Imaging must also be available, including X-ray, computed tomography, magnetic resonance imaging, and microbiological support services.

Multidisciplinary teams in the care of diabetes in pregnancy

Women of child-bearing age with diabetes should have access to pre-conception services (Chapter 71) [56]. Although they may be managed in primary care, it is essential that there is integration of care between primary care, community services, and specialist services. Specialist services can provide leadership and support to raise awareness and provide education to primary and community services so that women with diabetes are aware of the need for pre-conception counselling and support. Through this leadership, guidance, and auditing of clear documentation of pre-conception counselling, pregnancy care and post-pregnancy management can be carried out.

The components of a multidisciplinary specialist diabetes pregnancy service should include clear signposting to different aspects of care. These should include diet and lifestyle advice, provision of appropriate contraception, alcohol and drug counselling, higher-dose folic acid supplementation, smoking-cessation support, assessment and management of diabetes complications, setting of glycaemic targets, and regular discussion of results of self-monitoring. This will enable the woman to achieve as near-normal glucose levels as possible before conception. There should also be a discussion of diabetes pregnancy risks and expected management strategies and a clear documentation of care and counselling [57]. Once a woman with diabetes is pregnant, they should have access to a specialist multidisciplinary team with interest in diabetes in pregnancy, comprising obstetricians, diabetologists, dieticians, diabetes specialist nurses, and midwives. The role of the specialist multidisciplinary team should be to agree an individualized care plan covering the pregnancy and postnatal period up to six weeks. The details of the contents of such plans will be glycaemic targets, retinal and renal screening schedules, fetal surveillance, a plan for delivery, and plan immediate post-delivery diabetes care [58].

Multidisciplinary teams in the care of people with young-onset type 2 diabetes

With the rising prevalence of overweight and obesity, the prevalence of type 2 diabetes in the younger population is also rising (Chapters 69 and 70). An age of 40 years is a reasonable cut-off to classify the person with diabetes as young or old. People with type 2 diabetes under the age of 40 years have a fourfold increase in the risk of myocardial infarction compared with those diagnosed over

the age of 40 years [58]. This younger age group will also include women of childbearing age who require special care [59]. Diabetes occurring early in adult life appears to lead to more aggressive cardiovascular complications than in age-matched people without diabetes, although the absolute rate of cardiovascular disease is higher in older adults [58]. This cohort of individuals also has other intercurrent conditions such as psychological and mental health problems, non-alcoholic fatty liver disease, sleep apnoea, and vitamin D deficiency. The implications of this are not just the development of complications for these individuals, but a tremendous knock-on effect on the economy as a whole, as this is the age of heightened productivity. Hence strong leadership for the delivery and organization of services and championing of the needs of younger people with diabetes are essential. Younger individuals with type 2 diabetes require tailored management strategies to engage them and intensively manage their cardiovascular risk factors. This is because these risk factors are highly prevalent and insufficiently treated in this extreme phenotype of type 2 diabetes [60].

A service for young people with diabetes should include a consultant dialectologist, a diabetes specialist nurse, a specialist diabetes dietician, and a clinical psychologist with an interest in diabetes. The collaborative working of these healthcare professionals will ensure that a package of care encompassing the management of psychological issues as well as diet and cardio-metabolic risks is delivered. Younger individuals are likely to be in active employment and so flexibility in the delivery of service at the times conducive to them is essential for engagement, preferably through remote consultations. Telemedicine enhances service provision and quality of care, and mitigates service demand burdens. These individuals are kept connected to the healthcare system regardless of geographical boundaries. They also receive timely access to clinical care, with a reduction in the need for in-hospital care. In the primary care setting, there should be adequate provision for routine care, including diagnosis, initial management, continuing care, surveillance, management of complications, and annual assessment. Access to family planning, contraception, and preconception services must be provided. In working together with consultants, there should also be an agreement for arrangements for shared access to records and ready access to specialist diabetes advice. Targeted glycaemic levels can be aimed for before any attempt at conception is considered [56]. Access to smoking-cessation and substance abuse services should be integrated into any such service design.

Multidisciplinary teams in the care of older people with diabetes

Even though older people with diabetes have as high a risk of developing a spectrum of macrovascular and microvascular complications as their younger counterparts with diabetes, their absolute risk for cardiovascular disease is much higher (Chapter 72). Older adults with diabetes suffer excess morbidity and mortality compared with older individuals without diabetes [61]. Contributing factors to this increased risk include cognitive impairment, functional disabilities, frailty, polypharmacy, depression, urinary incontinence, and persistent pain [62].

The components of a diabetes service for older people should be commissioned, delivered, and monitored to ensure it is delivered as locally as possible, near to families' homes. The multidisciplinary staff members with an interest in diabetes must include a consultant geriatrician, a consultant old age psychiatrist, a diabetes specialist nurse, a consultant diabetologist, a specialist diabetes dietician, and a community pharmacist. Specific services aimed at older people with diabetes should include diabetes education programmes targeted to healthcare professionals looking after older people, because of the complexities of varying targets in this population [63]. Older people with diabetes are not a homogenous population; rather, they may include those who are functionally independent and residing in communities, or may be functionally dependent with many comorbidities and in assisted care facilities or nursing homes. Each group will have individualized targets for cardiovascular risk factor control. In frail older individuals with diabetes, avoidance of hypoglycaemia, hypotension, and drug interactions due to polypharmacy are of great concern [64]. This should be achieved without deterioration in HbA_{1c}, and with avoidance of falls and reductions in hospitalization [65]. In addition, management of coexisting medical conditions is important, as it influences the ability to perform self-management.

Suboptimally managed diabetes is associated with an increased risk for dementia, including the vascular and degenerative types. In addition, borderline and undiagnosed diabetes is related to Alzheimer's disease without vascular comorbidities, which suggests a direct link between glucose dysregulation and neurodegeneration [66]. Access to integrated memory clinics with psychological support and local counselling is therefore needed for older people with diabetes. Case management is best delivered by a dedicated community psychiatry nurse and a social worker who ensures that there is adequate provision for routine care, including diagnosis, initial management, continuing care, management of complications, and annual assessment. There should also be provision for rapid access to the service when needed, together with agreements with primary care for arrangements for shared access to records and 24-hour access to specialist diabetes advice. It may well be that due to the older people's multimorbid states and frailties, these services are delivered at home or in residential institutions. To facilitate this goal in this highly vulnerable population while continuing to provide the essential care, telehealth has emerged as a crucial care-delivery mechanism bringing specialty palliative care into the homes of seriously ill individuals [67].

Diabetes management can be discussed in advance and a virtual consultation session arranged later with the person with diabetes and their carer, during which a compliant teleconferencing application can be utilized to allow several healthcare professionals in separate locations to join a single virtual telehealth clinical encounter [68].

Staff composition of a multidisciplinary diabetes team

General or family practitioners

The use of primary care physicians (general or family practitioners) can be as good if not better than hospital outpatient care if regular review of the individual is guaranteed [3]. The enhancement of the generalist's care for people with diabetes by the use of quality improvement strategies, including audit and feedback, is an effective tool for reducing the cardiovascular risk profile [69]. The generalist's role often includes active case management of individuals with multiple conditions. In these groups, continuity of care is of paramount importance. Multidisciplinary primary care teams, led

by the generalist, therefore have a fundamental role in the prevention and identification of diabetes, as well as in routine care at a level that fits with their competencies. They will ensure that an accurate disease register is maintained to enable a call–recall system for annual reviews. They work cooperatively with other members of the team, seeking their views, acknowledging their contribution, and using their skills appropriately. Individuals with cardiovascular risk factors and those with early signs of microvascular complications can be identified and referred on to more specialist centres. The generalist has a more longitudinal relationship with individuals with chronic conditions including diabetes. They have the responsibility of coordinating the management of the person's acute and chronic complications of diabetes over time. They understand the individual in relation to their socioeconomic and cultural background and they recognize the impact of the problem on the individual's family and carers. They will therefore use appropriate support agencies, including primary healthcare team members, targeted to the needs of the person with diabetes.

The pay-for-performance initiative started in the UK in 2004 is probably the most ambitious quality improvement strategy and initially yielded some obvious improvements in the care of people with diabetes [70], but these benefits reached a plateau across the population [71] and did not lead to a reduction in variations in care [72, 73]. The organization of general practitioner specialist clinics in primary care has limited evidence in terms of the reduction of cardiovascular risk factors. The provision of primary care services for people with diabetes, whether from traditional general practitioner clinics or diabetes clinics run by general practitioners with a special interest, is effective in reducing HbA_{1c}, cholesterol, and blood pressure [74]. General practitioners are now managing people with diabetes and other complex comorbidities with complex therapeutic regimens.

Community pharmacists

A sustainable collaborative care approach for people with diabetes should make use of community pharmacists, who provide a local and accessible resource that is increasingly regarded as the first port of call for individuals with diabetes for help with the management of chronic disease. By offering programmes for monitoring therapeutic interventions, improving medication taking, and educating people with diabetes about their lifestyle, community pharmacists play a vital role in managing diabetes and its complications [75, 76]. On average, the community pharmacist consults with people with diabetes 3–8 times more frequently than other individuals [77]. As a result, in addition to bringing medicines expertise to the team-based care of people with diabetes and performing root-cause analyses of adverse events with diabetes medicines that contribute to the safety agenda, the community pharmacist can lead to a collaborative care approach of managing diabetes and reducing associated cardiovascular risk factors. The use of collaboration can bridge the gap between a successful pharmacy screening programme for diabetes and practitioner follow-up of these individuals [78]. This role can be extended to include individuals in residential care and housebound individuals.

Practice nurses

In primary care settings, chronic disease management is increasingly being performed by practice nurses, with general practitioners intervening only in complex cases [79]. In the case of diabetes, this has become even more necessary because of the increasing prevalence and burden of caring for people with the disease. Despite the worsening of health-related quality of life and an increase in diabetes-related symptoms, practice nurses can achieve results that are comparable to those achieved by a general practitioner in terms of cardio-metabolic risk factor reduction [79]. Individuals being treated by practice nurses also report being more satisfied with their treatment than those being treated by a general practitioner [79]. The care of people with type 2 diabetes can therefore be safely delivered by practice nurses using clinical guidelines. This makes the nursing team an important resource in a multidisciplinary primary care team. The extension of the practice nurse's role to include the initiation and titration of medications complements their other roles like supporting, educating, and enabling individuals to manage diabetes care, thus ensuring holistic delivery of care closer to home. However, practice nurses can potentially overutilize insulin inappropriately, although this can be limited by close collaborative working between nurses and doctors.

Diabetes specialists

Hospital diabetes clinics developed historically from the need for supervision of insulin treatment. Inevitably they also recruited large numbers of individuals not managed with insulin. The workload thus increased over the decades. With most people with diabetes now being managed in primary care, the specialist's role in insulin management has now been limited to acutely ill individuals with diabetes, including those with diabetic ketoacidosis or acute myocardial infarctions, intensive care–treated individuals, and those on renal wards who need meticulous insulin management to foster early recovery. Individuals with type 1 diabetes or type 2 diabetes who require very complex insulin regimens to manage their diabetes, for example those needing very large doses and those requiring insulin in combination with newer therapies, are best managed by a specialist [80, 81]. Most consultants with a specialist interest in diabetes are based in acute hospitals where they also deliver general medicine, alongside training roles, general management, and research. As a result of these multiple roles, they are well placed to provide multidisciplinary diabetes specialist teams with leadership though support and education to community diabetes services. In some areas the integration of services has made necessary the employment of an increasing number of community diabetes consultants who deliver and coordinate services in a community setting only.

Dietitians

The use of dietary education programmes improves anthropometric measures and glycaemic levels and the use of less prescribed medication [82]. By using improvements in people with diabetes' knowledge of how to self-manage their illness, dietician-led diabetes management programmes can be an effective strategy for glycaemic management and improving dietary habits for individuals with type 2 diabetes [83]. Registered dieticians contribute greatly to the comprehensive care plans of people with diabetes. They work as members of multidisciplinary teams across various healthcare settings, including primary and specialist care. Their caseload might encompass working with children, adults, young people, and individuals with mental health problems. They also have an important role in the management of those with diabetes and severe obesity. The dietician can offer support for the management of type 1 diabetes in areas around carbohydrate counting. In primary care, their role could be advising those at risk of diabetes and those with newly diagnosed diabetes on the appropriate dietary requirements. In the case of complex treatment conditions around a person with diabetes

needing initialization or augmentation of insulin therapy, dietetic support is normally needed. Within a specialist care setting they support antenatal and postnatal care of women with diabetes. In individuals with diabetes needing bariatric surgery, they can provide dietary support before and after the procedure. For individuals with mental health issues including eating disorders, dietetic support to maintain weight and glycaemic levels can be sought. On dialysis units and hospital wards, people with diabetes will normally need complex nutritional care, including enteral feeding. The dietitian supports people with complex problems such as gastroparesis and pancreatitis.

Community health workers

Diabetes programmes can include community health workers in the multidisciplinary teams in various roles. They usually reside in the target community and are given special training to help bring health services and education as well as health promotion to their local areas. They also mobilize members of the community to adopt behaviours that improve their overall health and living conditions [84, 85]. This important resource can lead to improvements in the individual's knowledge and behaviour and in some cases even improve biochemical outcomes in diabetes and promote health [86]. The optimal role of peer support of community lay educators is particularly crucial in low-income underserved populations, including racial and ethnic minority communities [87–90]. Community health workers' knowledge of their language, culture, and geographical communities can be used to coordinate care in partnership with healthcare systems [91]. Their functions include activities such as home visits, health education, and outreach activities for ambulatory care sites [85].

Conclusion

The management of diabetes through the integration of care between primary and specialist centres can result in the creation of new healthcare organizations that provide multidisciplinary diabetes care for their local population. These multidisciplinary teams work together around various areas of diabetes, including pregnancy, adolescence, and older people. Other groups of people with diabetes with specific needs are those with diabetes-related foot ulcers, kidney disease, and retinopathies. The teams comprise general or family physicians, community pharmacists, community health advocates, podiatrists, diabetes specialist nurses, and specialist diabetes physicians, all working seamlessly in a coordinated fashion in the different sectors of a diabetes service.

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75 Models of Diabetes Care in Low- and Middle-Income Countries

David Beran[1,2], Sigiriya Aebischer Perone[3], and Maria Lazo-Porras[4,5]

[1] Division of Tropical and Humanitarian Medicine, University of Geneva and Geneva University Hospitals, Geneva, Switzerland
[2] Faculty Diabetes Centre, Faculty of Medicine, University of Geneva, Geneva, Switzerland
[3] Division of Tropical and Humanitarian Medicine, Geneva University Hospitals, Geneva, Switzerland
[4] Division of Tropical and Humanitarian Medicine, University of Geneva, Geneva, Switzerland
[5] CRONICAS Centre of Excellence in Chronic Diseases, Universidad Peruana Cayetano Heredia, Lima, Peru

Key points

Overall Context

- Low- and middle-income countries (LMICs) will see the largest increase in diabetes over the coming years.
- These countries are characterized by lack of financial resources for health and weak health systems, resulting in overall low life expectancy.
- Beyond diabetes and non-communicable diseases, LMICs still face an ongoing challenge regarding communicable diseases.
- Different global declarations and strategies have been developed to address the challenge of non-communicable diseases including diabetes.
- Diabetes care in LMICs requires health systems to have a paradigm shift from providing acute to chronic care.
- Given the distinctions in burden, importance of primary prevention, complexity of management, populations affected, and need for insulin, different approaches are needed to respond to type 1 diabetes and type 2 diabetes.
- Health systems in LMICs are currently not prepared for the management of diabetes and other comorbidities.

Current Challenges

- An overall lack in numbers and of appropriately trained human resources is one barrier to diabetes management in LMICs.
- The data generated by the health system are rarely used to inform planning and responses as they are not collected for these purposes, in addition to there being a lack of research into various areas of diabetes in LMIC contexts.
- Availability and affordability of medicines, insulin, syringes, and blood glucose meters are all challenges in LMICs.
- Delivery of diabetes care is centralized in hospitals and main urban areas.
- Most guidelines in LMICs are inadequate in terms of applicability, clarity, and dissemination plan as well as socioeconomic and ethical-legal contextualization.
- As with guidelines, much of the information provided to people with diabetes is not adapted to the context or reality of LMICs.
- Overall financing for health is insufficient in LMICs with, in many cases, funding for healthcare being dependent on donors and their priorities.
- The global policy agenda for non-communicable diseases can be seen as focusing primarily on prevention versus treatment, as well as failing to provide adequate measures that can be implemented in LMICs.
- Specifically for LMICs, co-management and linkages of diabetes and diseases such as HIV/AIDS and tuberculosis need to be integrated into the health system's responses.
- Beyond disease-related factors, the specificities of vulnerable populations need to be considered.

Ways Forward

- Changes to the health system response will require changes at global, national, and health system level, including the driving principles of integration, continuity, universality, responsiveness, quality, and a focus on the individual.
- Global health policies and funding need to include the prevention and control of diabetes, foster civil society involvement, and work closely with communities.
- National policies need to address the issues of access to medicines, organization of care, human resources, and diagnostic tools.
- Health professionals will require training in diabetes and chronic disease management, including communication skills and patient education, with tasks being assigned to different professionals beyond doctors, including nurses, community health workers, pharmacists, and traditional healers.
- New approaches to data collection, analysis, and use are needed to help in programmatic planning, routine surveillance, and resource management.
- Access to affordable insulin and medicines needs to be guaranteed in addition to diagnostic tests and self-monitoring tools.

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- Continuity of care for diabetes includes the provision of comprehensive services and interventions addressing the health needs and the well-being of a person, from their diagnosis to possible provision of palliative care.
- Technology and innovations have the potential to have impacts on all aspects of diabetes care in LMICs, from data collection to education for individuals and possibly service delivery.
- Guidelines, information, and education on self-management for people with diabetes need to be adapted to the context between and within countries.
- Diabetes care in LMICs should be part of a universal healthcare package providing access to medicines and care at affordable or no cost to all individuals, including vulnerable populations.
- Quality mechanisms are required at the policy level and within the health system to guarantee quality control, including accountability measures for the health system and providers, as well as user-related outcomes and performance-based payments.
- The health system should be focused and organized around people, rather than diseases.
- Users of the health system should be included as active participants in the delivery of services and should have channels to actively voice their concerns, to shape health services and policies, as well as to hold health providers and policy makers accountable.

Low- and middle-income countries (LMICs) are defined by the World Bank as countries with an income per capita of less than US$4045 per person per year [1]. This group comprises 79 countries including Afghanistan, Algeria, Ecuador, Kyrgyzstan, India, Malawi, and Vietnam, with 53% of all countries in the category being located in the World Health Organization (WHO) Africa region. LMICs represented 47% of the total global population in 2019 and in 2018 average life expectancy at birth in these countries was 66.1 years, in contrast to 72.6 years globally and 80.7 in high-income countries (HICs) [2]. There is a noteworthy difference in health expenditure per capita between LMICs and HICs, with on average LMICs spending US$93.4 (range US$19.4 in the Democratic Republic of Congo to US$424.8 in the Federated States of Micronesia) in contrast to US$5244.1 for HICs.

Globally, it is estimated that 463.0 million people had diabetes in 2019, with this predicted to increase to 578.4 million in 2030 and further to 700.2 million in 2045, with the largest increase in LMICs [3] due to ageing populations, lack of physical activity, and unhealthy nutrition attributed to rapid urbanization [4]. People with type 2 diabetes in LMICs represented 33% of global cases in 2019, and 30% of the estimated 1.1 million children and adolescents (aged 0–19 years) with type 1 diabetes live in LMICs. Therefore, the countries facing the largest increase in the diabetes burden are also those with the health systems that are the least prepared to face this challenge [5].

To respond to the diabetes challenge different global initiatives have been developed. This includes the United Nations' Sustainable Development Goals (SDG) and the WHO's Global Action Plan for the prevention and control of non-communicable diseases (NCDs). At a global level the diabetes agenda is combined with that of NCDs, which for the WHO includes cardiovascular diseases, cancers, chronic respiratory diseases, and mental health conditions. Targets included in these documents include access to medicines, universal health coverage, and decreases in premature mortality. However, very little focus is given to addressing the weaknesses that exist with regard to delivery of diabetes care by health systems in the global diabetes response [6–8]. Therefore, LMICs and their health systems need to address the increasing burden of NCDs in parallel to managing the existing populations with diabetes [4, 6]. This is especially challenging as health systems in LMICs are not adapted to manage chronic conditions, but rather acute diseases [8, 9]. The coexistence of NCDs and communicable diseases, the so-called double burden of disease, means that different needs and health system approaches are required to address the healthcare of populations [10]. However, there are synergies, as many communicable diseases can be viewed as chronic, such as HIV/AIDS, or have chronic sequelae, such as some neglected tropical diseases [11, 12].

The WHO defines the primary role of the health system as 'to promote, restore and maintain health' [13]. Six components, or building blocks, make up the health system [13]:

- *Healthcare workforce*: the human resources and how they are trained and used to deliver specific services to the population.
- *Information*: data collection and generation by the health system and how these data are used to inform different decisions, as well as how research can help guide health system responses.
- *Medical products, vaccines, and technologies*: how medicines and necessary products are delivered to individuals and issues around their availability and affordability.
- *Service delivery*: how care is delivered.
- *Financing*: how healthcare is financed in a given context – people paying out of pocket for their care, tax-based systems, insurance schemes, etc.
- *Leadership and governance*: how the health system acts as a political actor in shaping health-related policies beyond the immediate health sector.

Each health system is different and its organization is linked to other sociopolitical factors in a given country, meaning that countries take different approaches in delivering each of these components [8].

In responding to diabetes as a whole, it is important to distinguish the health system response for type 1 diabetes and type 2 diabetes. The burden of type 2 diabetes is much more significant than that of type 1 diabetes. For every person with type 1 diabetes there are 455 with type 2 diabetes in LMICs [3]. Different approaches are needed from the health system perspective in addressing these two types of diabetes. First and foremost is the health system's role in prevention. Type 2 diabetes, given its close links with obesity and other common NCD risk factors, requires the health system to play an active role with regard to influencing policies external to the delivery of care, as well as the system playing a vital role in prevention. There is a push by the WHO to decentralize the care of type 2 diabetes to primary healthcare settings and involve the community [14, 15]. Beyond this, there is also the need to ensure that quality of care is improved and that health systems are capable of responding to the complex needs of the populations they serve [16].

In contrast, prevention of type 1 diabetes is not feasible and, in many settings, it remains a condition managed by specialists in tertiary facilities [17, 18]. There are two other important differences between type 1 diabetes and type 2 diabetes from a health system perspective. First, type 1 diabetes is mainly diagnosed in younger populations, although an increase in obesity and type 2 diabetes in

children has been reported even in LMICs [19]. Next, for type 1 diabetes access to insulin is a life-or-death situation, in contrast to type 2 diabetes where insulin is needed for better management. Given these differences, approaches to managing type 1 diabetes and type 2 diabetes from a health system perspective need to address the six building blocks in different ways. That said, many similarities exist with regard to the need for continuous access to medicines, trained health personnel, and the importance of education and empowerment [20]. Another key component is guaranteeing that the financial cost of care and medicines is not a barrier.

What are the current challenges of managing diabetes in low- and middle-income country settings?

Management of diabetes and its coexisting conditions requires long-term care and follow-up of individuals by a trained interprofessional team of healthcare workers, access to medicines and diagnostic tests, empowerment and education of people with diabetes and communities, prevention of cardiovascular disease, information and data management, treatment of complications with referrals between different levels of the healthcare system, including end-of-life care, and coordination between all stakeholders [8, 21]. In comparison to HICs, additional challenges in the management of diabetes in LMICs include low implementation of policies, the lack of trained health professionals and staff shortages, low availability and high prices of medicines and diagnostic devices, consultation fees, and the general economic vulnerability of populations [6, 8, 22–24]. Beyond these factors the overall health systems in LMICs require a paradigm shift to move from providing acute to chronic care [25–28]. Although this challenge is global, the main barrier to implementing the changes needed in LMICs to improve chronic care is linked to the availability of resources [29].

Human resources, information, and medical products

Looking at human resources, the issue faced by LMICs is both in connection to numbers of professionals within the system and the training they have with regard to diabetes [30]. This is especially true for specialists, with few diabetologists present and these mainly being in major urban areas [20]. In addition, due to its low prevalence many health professionals will be unfamiliar with type 1 diabetes. Surveillance systems are scarce in many LMICs. Much of the data collected at facilities and for individual patients are paper based, with the data generated by the system rarely used to inform planning and responses [8, 30, 31]. Beyond this information generated within the health system, studies are lacking on the diabetes burden, especially type 1 diabetes, and understanding this condition in LMIC contexts [6, 32].

Availability and affordability of medicines, insulin, syringes, and blood glucose meters are challenges in LMICs [23, 33–35]. Availability has been found to be affected by the level of the health system (hospital vs primary healthcare), location (urban vs rural), and sector (public vs private) [6, 23] (Figure 75.1). A wide variation in ministry of health/government purchasing prices has been found [34, 36] (Figure 75.1), which can have an impact on the affordability to the health system [37]. For the individual, mark-ups in the system further affect the affordability of medicines [38]. Affordability for the individual can vary widely, with prices in the private sector being significantly higher than in the public sector. In contrast to HICs, people in LMICs are less able to afford medicines for diabetes, with 27% of households in LMICs unable to afford metformin in contrast to 0.7% in HICs [35]. The same is also true for insulin, with 63% of people with diabetes unable to afford insulin in LMICs, versus 2.8% of people in HICs. The difference in affordability of metformin versus insulin also raises the issue of the impact of different treatment regimens on the overall cost of care for the individual. Globally, one in two people with type 2 diabetes requiring insulin cannot access it, whereas in sub-Saharan Africa this is one in seven people [39]. This highlights a variety of health system factors, including the existence and use of guidelines, healthcare worker training, and the availability and affordability of insulin, which influence overall access and ultimately management and outcomes.

Delivering diabetes care

With regard to the delivery of diabetes care, there is a need to look at the overall organization of care within the health system as well as the organization of the consultation. In many LMICs the

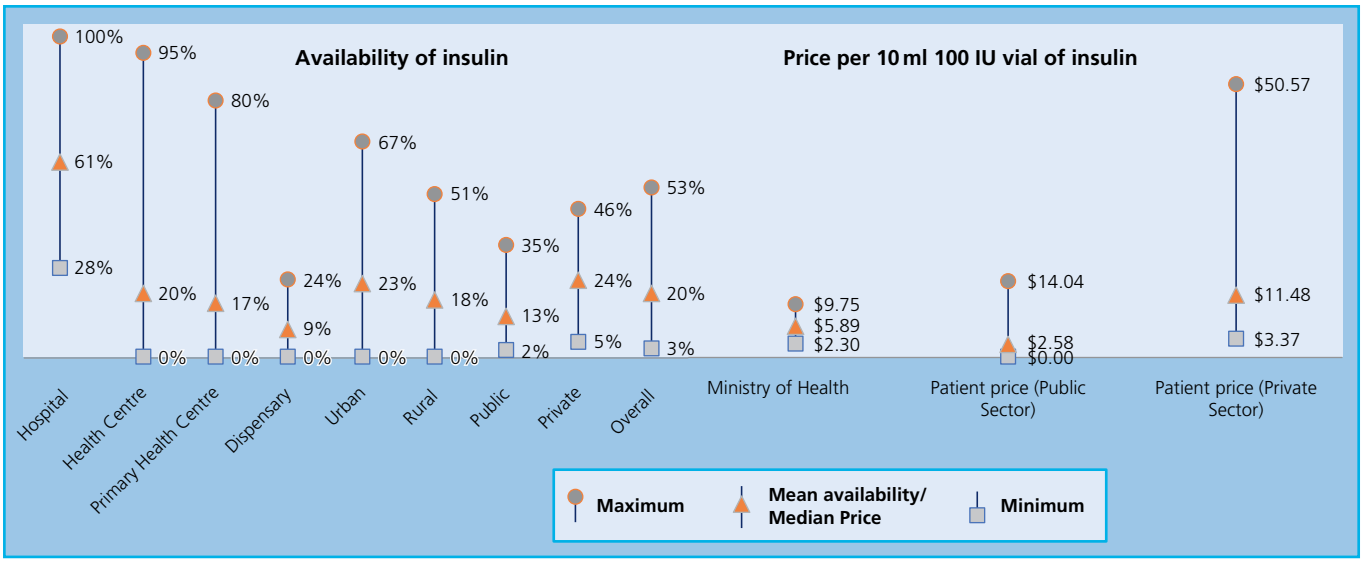

Figure 75.1 Availability and price of insulin at different levels of the health system. Source: Data from Atun et al. 2017 [6].

management of diabetes is centred at hospitals [17, 40], despite WHO guidance focusing on the importance of primary healthcare [14, 15]. Although primary healthcare is seen as a tool to address the majority of the health needs of an individual throughout their life [41], as well as being the focus of renewed political interest in 2018 with the Astana Declaration [42] to celebrate the 40th anniversary of the Alma-Ata Declaration, there has been insufficient investment in primary healthcare and human and material resources are lacking at this level of the health system for appropriate diabetes care [16, 43, 44]. Beyond defining the role of each level of the health system and ensuring that the appropriate resources are available to manage diabetes, challenges exist with regard to the referral system from primary healthcare to hospitals, as well as counter-referrals from hospitals back to primary care [20, 43]. This is especially important for the management of diabetes-related complications. Many services for the diagnosis and care of diabetes are lacking in most LMICs at primary healthcare level and are only available in major hospitals [6].

One issue with the delivery of diabetes care in LMICs is the adaptation and use of clinical guidelines. The WHO's Global Diabetes Report highlights that 71% of countries have a national guideline for diabetes management that is either fully or partially implemented [4]. It has also been reported that most LMIC guidelines are inadequate in terms of applicability, clarity, and dissemination plan, as well as socioeconomic and ethical-legal contextualization [45]. In comparison to guidelines developed and used in HICs, the range of elements included in LMIC guidelines was seen to be limited and the process of development as suboptimal, as well as not following guidance as to what should be included in guidelines.

A key component of diabetes care is information and education about diabetes and how the individual needs to manage their condition for proper self-management. As with guidelines, much of the information provided is not adapted to the context or reality of many individuals with diabetes in LMICs [46, 47]. This was especially true with regard to dietary and physical activity recommendations [46], as well as there being a lack of focus on psychosocial issues [47]. The result of this is that people with diabetes are less likely to follow advice about self-monitoring of blood glucose, physical activity, diet, and medications [47]. Many of these factors are also linked to the availability and affordability of medicines and care. Another factor to consider is the importance of traditional healers and their role in the overall health system [20].

Specifically for type 1 diabetes, different initiatives have enabled the establishment of specific delivery of services, but these focus on children and adolescents and rely on external donations and support for their implementation [48]. This is a problem, as when these young people graduate from these programmes they are unable to afford insulin or other supplies.

Financing and leadership

Overall financing for health is insufficient in LMICs [2] and this is a key element to be able to deliver adequate diabetes care [29]. Funds for healthcare in many LMICs are also dependent on donors and their priorities. Development assistance for health represented 25% of health expenditure in LMICs, totalling US$38.9 billion in 2018 [49]. However, 2% of this amount was allocated to NCDs, with the majority of this funding being apportioned to maternal and child health and communicable diseases. Much of the funding allows for treatments, for example for HIV/AIDS, to be provided for free, in contrast to diabetes care that needs to be paid for out of pocket [6, 50]. In LMICs 60% of healthcare costs are borne by the individual through out-of-pocket payments, in contrast to 20% in HICs [29]. Beyond this funding for care, budgets to address NCDs and diabetes within national programmes are lacking. For example, in 2010 only US$97 000 was allocated to the NCD Department within the Ministry of Health in Mozambique [51] and in Peru 3.2% of the total budget was allocated to NCD programmes, despite this group of diseases representing 66% of overall mortality.

The global policy agenda for NCDs can be seen as focusing primarily on prevention versus treatment, as well as failing to provide adequate measures that can be implemented in LMICs [7]. A study found that 88% of 156 countries examined reported having a national diabetes policy, plan, or strategy [4]. Overall, only 77% of these were funded and implemented, but for LMICs this was less than 60%. A summary of all the challenges present for the health system response in diabetes in LMICs is presented in Table 75.1.

The health response cannot only focus on diabetes

In responding to the challenge of diabetes, the health system response needs to include other health challenges that people with diabetes will face, as well as specific responses to certain populations.

Diabetes and comorbidities

Comorbidities are frequent in individuals with type 2 diabetes, as well as being more numerous in socially deprived individuals, and influence their quality of life [52, 53]. Due to the shared risk factors between type 2 diabetes and other NCDs, people with type 2 diabetes have a higher risk of developing another NCD as well as mental health problems. While the negative interaction between depression and diabetes has been widely studied in HICs, only a few studies have examined the comorbidity of depression in people with diabetes in LMICs, which have an estimated average prevalence of depression of 36%, higher than in HICs (25%) [54].

Beyond this interaction between diabetes and another NCD, there is the additional challenge of the links between diabetes and communicable diseases, such as tuberculosis and HIV/AIDS. People with diabetes are more susceptible to tuberculosis infection [55]; and the actual treatment regimen for HIV/AIDS can lead to the development of diabetes [56]. There is not only the increased risk of these disease interactions, there are also poorer outcomes for people with diabetes affected by communicable diseases [55]. Part of this is due to the fragmentation of care for diabetes and communicable diseases, with diabetes and tuberculosis management for example in Kyrgyzstan being completely separate, leading to increased cost and burden of care for individuals [57].

The Covid-19 pandemic has brought to the forefront the challenges of the continuity of diabetes care as well as the increased risk of people with diabetes suffering negative consequences from a concomitant disease [58–60]. A rapid assessment conducted by the WHO highlighted a disruption to NCD services in three-quarters of countries in all regions and income groups [61]. The impact of Covid-19 was manifold. It affected continuity of access to care due to lack of protective equipment, stocks of medicines, and lack of health workers, in addition to lockdowns prohibiting movement of staff and people and leading to closure of health facilities. In addition, the Covid-19 pandemic influenced the ability of countries to continue to give access to essential health services providing care for diabetes, putting people with diabetes at risk of interruption of treatment and complications. Confinement also meant impacts on diet, physical activity, and mental health, as well as possible delays in seeking care or accessing necessary medicines and supplies,

Table 75.1 Summary of barriers to diabetes management in low- and middle-income countries.

	Healthcare workforce	Information	Medical products	Service delivery	Financing	Leadership and governance
Health system building block	• Lack of human resources • Lack of training • Lack of task shifting/sharing • Non-inclusion of traditional healers/ medicine in health system responses • Lack of role for pharmacists	• Lack of tools for data collection, analysis, and use	• Availability and affordability of medicines • Availability of diagnostic and monitoring tools	• Overall organization of care • Centralized care in urban areas • Hospitals versus primary care • Lack of adapted guidelines and implementation • Poor integration of education and empowerment activities	• Predominantly out of pocket • Lack of funding of national programmes	• Health system's role in prevention • Lack of policies and strategies • Poor integration of other sectors

Underlying factors

- Overall rates of poverty and socioeconomic conditions with competing priorities
- Rapid epidemiological changes
- Environmental factors, e.g. access to food and opportunities to be physically active
- Low health literacy
- Cultural constructs of diabetes as a disease/stigma
- Low healthcare funding
- Donor agendas
- Persistence of communicable diseases

either due to government lockdown measures limiting movement or individuals' fears of contracting Covid-19 within the health system [59, 60]. An additional challenge is that the Covid-19 response focused on hospitals, which are usually where diabetes care is provided, thus further limiting access. Beyond these factors specific to diabetes, vulnerable populations also faced financial hardships due to the pandemic further affecting their access to medicines and care.

Specific challenges for vulnerable populations

Covid-19 also brought a spotlight to the challenge of specific populations who can be considered vulnerable and who are often forgotten by health systems, who face additional challenges due to 'individual factors such as sex, age, race, gender, ethnicity, displacement, disability and health status' [62]. For example, in sub-Saharan Africa a higher prevalence of overweight, obesity, and diabetes is found in women versus men [6]. Differences are also seen between men and women when it comes to health-seeking behaviour [63]. Ageing populations are a challenge in LMICs, with a faster rate of ageing than that seen in HICs as well as a lack of mechanisms in place to support this growing proportion of the population with a wide range of health and social needs [64].

Although a paucity of data exists in LMICs for specific vulnerable populations, studies from other contexts shed light on the challenges, for example for Indigenous populations with regard to access to services. In Guatemala a variety of challenges were faced by Indigenous populations in their access to diabetes care, ranging from preference for Indigenous languages over Spanish, lack of knowledge and medical constructs around diabetes and chronic disease, access to medicines, and use of traditional medicine [65].

Migrants are another vulnerable group. Migration has an impact both on the development of diabetes and on access to services [66, 67], with some studies showing that rural-to-urban migration leads to an increased prevalence of diabetes [68] in LMICs. Most studies on migration and diabetes are from HICs, showing higher rates of diabetes and poorer access to services for migrant versus host populations. These phenomena are probably also present in LMICs for both internal migration as well as people migrating across borders.

Another population to consider is the 125 million people affected by humanitarian emergencies [69]. In these settings, health actors and individuals face challenges providing health services with security and safety concerns, destruction of health facilities, migration and death of health personnel, interruptions in supply chains, and sanctions preventing import of certain equipment and supplies [70].

Inter- and intra-country disparities exist and are driven by the social determinants of health, which are themselves clear drivers of the diabetes epidemic and need to be addressed by the health system [71]. The WHO defines social determinants of health as 'the conditions in which people are born, grow, live, work and age. These circumstances are shaped by the distribution of money, power and resources at global, national and local levels' [72]. In tackling the social determinants of health, the health system actually plays a small role (10–15%) in influencing health outcomes, in contrast to 50–60% that is shaped by social and environmental factors [73, 74].

The issue of equality and the impact of health system gaps

From a global perspective, the situation of both type 1 diabetes and type 2 diabetes highlights global inequalities in access to medicines and care as well as financial protection [75]. This is especially striking for type 1 diabetes, where 2021 marked the centenary of insulin's discovery, yet lack of access to this life-saving medicine still results in life expectancy in LMICs being substantially lower than in HICs [18, 33]. Beyond global inequalities, national inequalities also exist, with better access to diabetes care and medicines in urban versus rural areas [24].

Many HICs provide care for free or at least financial protections to their populations to try to reduce these inequalities [37]. In many LMICs these protections do not exist, and if they do they do not cover all those with diabetes, as many are undiagnosed. In addition, financial protections will be challenged in the future by the increasing burden of diabetes [37]. For example, in Nicaragua care is provided for free to individuals with diabetes. However, diabetes accounted for 5% of the total healthcare budget, even though only one in five people with diabetes was actually diagnosed and managed by the system.

The impact of these gaps results in 48% of NCD-related mortality in LMICs being premature (occurring before the age of 70 years) in contrast to 42% globally, with diabetes causing 4% of these deaths [76]. For type 1 diabetes life expectancy is extremely low in LMICs [20], with for instance one in six people with type 1 diabetes dying within five years of their diagnosis in the Democratic Republic of Congo [77].

This high rate of mortality is due to poor control and lack of access to medicines and care [20] affecting diabetes self-management. For example, in a cohort of people with type 1 diabetes in Tanzania, glycated haemoglobin (HbA_{1c}) was rarely done, but for those individuals where this was measured, the mean HbA_{1c} was 11.1% [78]. This sub-optimal glycaemic management resulted in 22% of this group of individuals having retinopathy and 29% neuropathy, even though the cohort was young (mean age 21.1 years) and had had type 1 diabetes for a relatively short period of time (6.2 years). For type 2 diabetes diagnosis may happen later in the disease progression, with many people being diagnosed already having a complication [6]. In sub-Saharan Africa a wide range of rates of complications has been found, ranging from 7% in Kenya to 63% in South Africa for retinopathy, from 27% in Cameroon to 66% in Sudan for neuropathy, and from 10% in Tanzania to 83% in Nigeria for microalbuminuria.

There are differences in the cascades of care for type 2 diabetes between people who are aware of their diabetes status, those treated for their diabetes, and those who have well-managed diabetes. Figure 75.2 shows that for many LMICs under 60% of people with diabetes are actually aware they have diabetes, and many of those under treatment are not reaching glycaemic targets [79, 80]. In looking at the data in Figure 75.2 for India, sex and geographical differences can be seen, with women being more likely to be aware, treated, and within target in comparison to men, and people in urban areas faring better than people in rural areas [79]. This highlights the different challenges faced by different populations within the same context, as discussed in what follows.

What are the ways forward?

Looking at the cascades of care, the focus could be on increasing detection of people with type 2 diabetes through screening programmes, although this is not recommended by the WHO [81]. Another approach could be to ensure that all those diagnosed with diabetes are given treatment, but as presented in the previous section, the challenges are significant. The final approach for type 2 diabetes would be to improve services for those already accessing care and medicines and improve overall rates of optimal diabetes management. This would ensure that the investment by the health system and/or the individual in spending resources on medicines, testing, and consultations is utilized optimally, in parallel to building and strengthening the foundations of the delivery of diabetes care for the benefit of people with both type 1 diabetes and type 2 diabetes. Guaranteeing access to insulin and strengthening services for type 1 diabetes through different support programmes has shown a positive impact in terms of survival [82], but challenges remain with regard to glycaemic management [78, 83, 84]. Besides improving care, there is also clearly a need to stem the rising prevalence of type 2 diabetes in LMICs, and this requires the health system to widen its remit and stewardship in influencing other sectors to address the determinants of diabetes.

First and foremost, global health policies and funding need to include the prevention and control of NCDs, including diabetes. The WHO's 2016 Global Diabetes Report (Box 75.1) provides a list of recommendations building on the Sustainable Development Goals and other global commitments. These are far ranging, but highlight the complexity of the issues at hand and that a holistic global policy approach is needed, including early childhood interventions, fiscal policies, and guaranteed access to essential

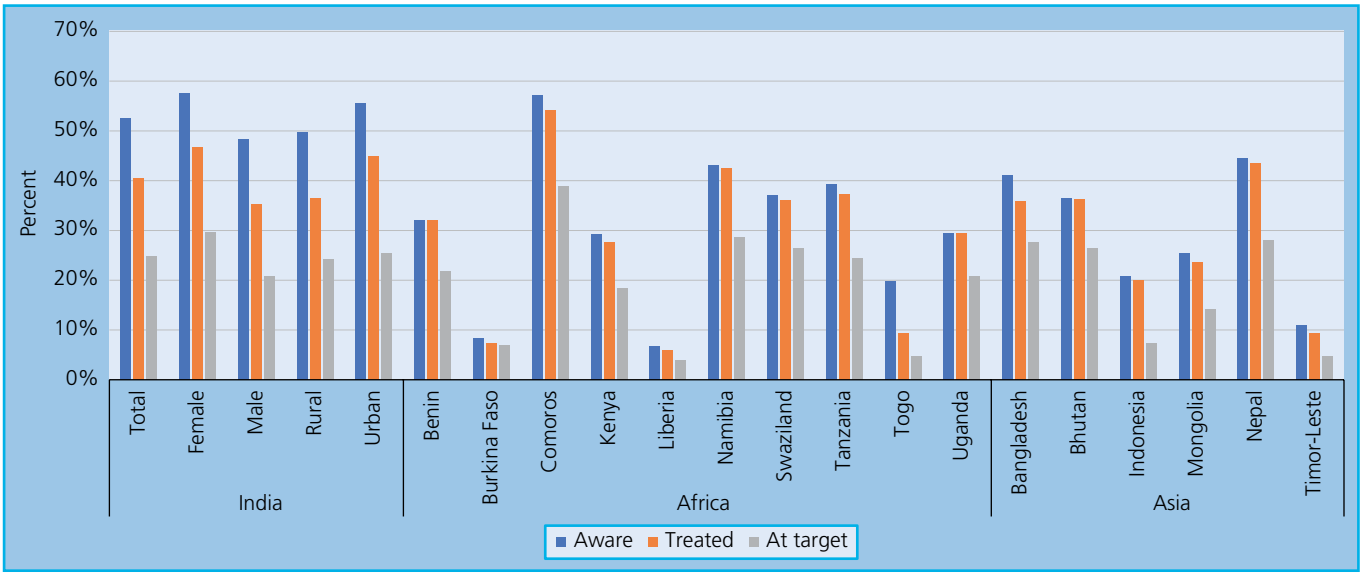

Figure 75.2 Cascades of care for different low- and middle-income countries. Source: Data from Prenissl et al. 2019 [79] and Manne-Goehler et al. 2019 [80].

Box 75.1 World Health Organization global diabetes report

Prepared in 2016 to commemorate World Health Day, the World Health Organization's Global Diabetes Report proposed the following recommendations.

At a policy level

- Create multisectoral commissions at a national level.
- Strengthen ministries of health in their capacity to engage different partners.
- Monitor and evaluate processes established to increase accountability.
- Develop and implement national policies and plans.
- Prioritize preventive measures to address overweight and obesity, including before birth and in early childhood.
- Promote healthy policies and programmes including breastfeeding, addressing the consumption of unhealthy products, such as sugar-sweetened beverages, the built environment, and physical activity.
- Use taxation as a tool to help with this.

At a health system level

- Reinforce health systems, specifically in primary care.
- Develop guidelines and protocols.
- Improve access to medicines and technologies for diabetes management.
- Improve data collection systems and establish diabetes registers.

Source: World Health Organization 2016 [4].

medicines and technologies. Although these are proposed for individual countries, they require global support in order for them to be implemented. At a global level the inclusion of insulin in the WHO's prequalification programme to guarantee quality products on the market and increase competition [85] is a good example of a global measure with possible wide ramifications in particular countries.

For LMICs, changes to the health system response to diabetes will require changes at global, national, and health system level. At each of these levels addressing the growing burden of diabetes as well as access to effective care, including of vulnerable populations, will be needed, with aspects of integration, continuity, universality, responsiveness, quality, and a focus on the individual as driving principles to change the way health systems operate.

Integration as a solution

There are different perspectives on the concept of integration. Integration can happen at policy, health system, or individual levels [86]. From the global level, integration is how to ensure that different health problems are addressed together rather than in silos [87]. Many successes in LMICs, for example regarding HIV/AIDS, have taken a vertical approach where all elements of the health system were strengthened for this health issue, versus taking a horizontal approach and using the resources for HIV/AIDS for all health needs [88]. Any solution will require a health system strengthening versus a health system support approach [89]. Strengthening a health system requires depth in providing more than simple inputs and breadth so to address more than one specific issue, as well as ensuring that all elements are integrated into the formal health system. One example of health system support activities is the various donation programmes for type 1 diabetes that exist and, although they have had an impact, have yet to be fully integrated into the health system response for diabetes [48].

At a national level, integration needs to happen at the policy, health system, and community levels [9]. The WHO has developed the concept of 'health in all policies' [90], which for diabetes would mean that a wide range of other sectors would be involved in addressing this challenge. This integration of different stakeholders and sectors to address some of the complex issues at hand would also need to include the private sector when looking at issues of access to medicines and technologies. For other diseases affecting LMICs the private sector has played an active role in addressing the challenge [91] and it might be able to also do this for diabetes. It has been proposed in general with regard to delivering health services that private healthcare providers could also play a part in delivering universal health coverage [92].

NCD policies at a national level need to expand beyond health and experts, and foster civil society in order to develop a broader and more inclusive governance structure [7]. Most NCDs, including diabetes, cannot be solved without addressing their determinants, and these determinants lie beyond the health sector and require the involvement of other sectors [93]. In order to operationalize and foster accountability, it is important to invest resources in the development and implementation of policies with clearly established indicators [4]. For example, in order to achieve its goal to improve the health of the population by reducing premature mortality from NCDs by 15% by 2020, Azerbaijan established a high-level national intersectoral coordination mechanism with the involvement of the following sectors: social, agriculture, finance, trade, transport, urban planning, education, and recreation [93]. Interactions with civil society and the private sector are also part of this platform.

There are two main measures at the policy level to prevent diabetes and NCDs that have been implemented in LMICs, and especially in Latin America, which call for such intersectoral collaboration. One policy intervention is front-of-package nutrition labelling and secondary taxation of sugar-sweetened beverages and non-essential energy-dense foods. Another area is the removal of different tariffs and taxes on medicines [38]. These policies require the health sector to work with, for example, the ministry of finance both to use these policy measures to prevent diabetes as well as to generate additional income. The examples of Hungary and Mexico show that taxes on sugar-sweetened beverages were able to decrease the consumption of these products as well as generate additional resources for health [94–99].

In focusing on integration and the delivery of care, the WHO proposes two definitions that include access to care when needed. Care should be user-friendly, focusing on the individual's needs, including a range of preventive and curative services delivered over time and at different levels of the health system, and it should result in positive outcomes and be affordable [87]. This would mean that integrated diabetes care would provide a one-stop shop for all the needs of the individual through a package of defined services that would be made available [87]. In HICs, integration of care often focuses on the delivery of health services in conjunction with social care [86, 100–102]. The areas of integration in HICs include human resources, for example the role of nurses [103–110]; how complementary and alternative medicine can be integrated with allopathic approaches [111];

or the role technology can play in integration [112–123]. In contrast, studies on integration in LMICs have focused on four main areas of integration: integration between services for two separate health issues [124, 125]; using existing services to integrate a new response [126–130]; integrating communities as providers of health services [131–133]; and use of primary healthcare as a platform for integration between different diseases [134, 135].

Looking at the specificities of integration for type 1 diabetes, the focus of integration is around seamless transition through services catering to the different ages of people with diabetes, from paediatric to adolescent and finally adult care [136]. The two other elements addressed with regard to integration are specialists [137] and addressing psychosocial issues [138]. At the level of the health system, one such example of integration from Cameroon was integrating traditional healers in a wide range of roles in diabetes care [139].

To move diabetes care forward in LMICs, integration is needed in its most holistic sense, with the concept of packages of services being delivered, a focus on the individual, links between what is provided by the health system and the population's needs, and the use of interprofessional teams [140]. This can also include bundling of interventions, services, and even medicines and tools. That requires both horizontal integration to link different services within the same facility as well as vertical integration between different levels of the health system. The aim of this integration is to address not only diabetes, but also the full range of health needs an individual may have.

Continuity in addressing the needs of the individual and continuity of care

The aim of integration of care is to ensure continuity of care [86], which from a health system response is another guiding principle for diabetes care in LMICs. This continuity can be seen as continuity over the life course of the individual to avoid exposures to diabetes risk factors at different ages, for instance proper maternal nutrition, breastfeeding, access to food, and proper living conditions during childhood, adolescence, and adulthood. This can be seen as the public health role of the health system. In parallel, there is a continuum of care, an element defined as 'Access to comprehensive services and interventions that address the health needs and the well-being of a person, from the identification of a health condition until the recovery of a functional state consistent with the context' [141]. It focuses on ensuring that those individuals receiving treatment within the health system do so in an optimal way.

Continuity of care is also valued by individuals with diabetes with regard to having regular periodic checks, support and education, developing a relationship with their providers, the services they receive adapting to their needs, and having the same staff care for them and coordinate the services they receive in different health facilities [142]. Such continuity requires the health system to provide continuous access to care, medicines, and diagnostic tools over time and at different levels of the health system [29]. While most people with type 2 diabetes can be followed within primary care, there is still a need to guarantee access to ancillary and specialized services. These services should include for example mental health support, referral to hospital, rehabilitation, and palliative services. Due to access issues especially in rural areas, telemedicine and other options are needed. Palliative care for diabetes in LMICs should be included, due to the lack of services to manage complex complications such as end-stage renal failure. This continuity also needs to go beyond the health system and incorporate the community, which can play a role in the promotion of healthy lifestyles, initiation of treatment, continued monitoring and medication taking, and long-term follow-up [143]. This role for the community needs to be integrated within the health system and also allow for certain tasks to be shared or shifted from healthcare providers to community members, given the human resource challenges in LMICs. Many national programmes for NCDs in LMICs involve community health workers, who are lay health workers based in the local community. They are frequently involved in prevention (lifestyle modifications) and possibly screening as part of early diagnosis and management [144]. Their involvement together with peer supporters in the self-management of diabetes appears to show some improvements in outcomes. However, the effectiveness of the intervention of this heterogeneous group, with differences in training, supervision, and type of peer support (e.g. face-to-face home visits vs telephone) needs to be further evaluated [145].

Universality in access

Diabetes-related tools should be part of the defined universal health coverage package. In order to achieve this additional funding is necessary in LMICs, but with the aim of caring for the highest possible number of people by making rational choices in using resources. For example, in Kyrgyzstan in 2009 close to US$740 000 was spent on analogue insulin, which at this time was not included on the WHO's Model Essential Medicines List, equivalent to government spending for 20 000 people. The United Nations (UN) in the Sustainable Development Goals as well as during a special high-level meeting in 2019 has called for universal health coverage to be a driving force of the global health agenda [146]. Within the Sustainable Development Goals, the target is to 'Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all'. Within this element two components are important, namely financial protection and coverage of services [147], as well as the funds made available for universal health coverage through different sources [148].

Beyond universal coverage there is also the issue of universality of access in a given context, with different diseases given different priority in different settings. For example, in Cambodia the inequity between people receiving free treatment for HIV/AIDS versus people with diabetes needing to pay for their own care out of pocket resulted in people with diabetes 'wishing they had AIDS' [149].

Quality and responsiveness as driving principles

Improving quality requires policy and system responses [16]. There is a need to have quality mechanisms in place at the policy level and within the health system in order to guarantee quality control, including accountability measures for the health system and providers, as well as user-related outcomes and performance-based payments [9, 16]. Supportive supervision is a key to guaranteeing quality and reinforcing training [150]. This includes measuring the patient experience [88] as well as audits [125]. With regard to healthcare services, quality of care is having present all the elements needed for the proper management of diabetes, from guidelines to trained health professionals, diagnostic tests, and so on, but also the experience of receiving healthcare by the individual [16]. Quality of care includes the notions of being valued, trusted, and adapting to the different needs of people using the health system. Quality of care needs to enhance the services provided to address these three elements.

Aligned with quality improvement is the concept of responsiveness put forward by the WHO, which addresses how well health

systems respond to the expectations of the populations they serve, focusing on the experience of care [151]. Responsiveness, as defined by the WHO, is the 'outcome that can be achieved when institutions and institutional relationships are designed in such a way that they are cognizant and respond appropriately to the universally legitimate expectations of individuals' [151]. Responsiveness includes eight elements: dignity, autonomy, confidentiality, clear communication, prompt attention, quality of amenities, access to social support networks, and choice of self-provider. The concept of trust is also sometimes included as a further element of responsiveness [152]. The main aim of this approach is to focus health system responses on the service experience of individuals [151].

There are four types of continuity that have been described and all of these have a link to the delivery of quality services and guaranteeing that services are responsive. There is longitudinal continuity (the follow-up over time of the individual); relational continuity (having a relationship with the provider[s] that goes beyond just a clinical consultation); flexible continuity (services evolving with the individual); and team continuity (coordination between the different providers and services that the individual needs) [142]. All of these require a quality focus as well as being essential for quality healthcare to be delivered.

A focus on the individual

Health system responses need to focus on the individual, as chronic diseases can be described from the perspective of the individual as a biographical disruption [153], with all elements of daily life being affected by diabetes, such as taking medicines, changing lifestyles, and so on. These changes have been described as needing three 'overlapping galaxies' [154, 155]. The first galaxy is the role individuals themselves need to assume in caring for themselves, taking medicines, and changing their lifestyle. Health professionals comprise the second galaxy by working in interprofessional teams meeting the wide range of care needs the individual may have. Society as a whole is the third galaxy, which has to provide a propitious environment for the individual to manage their chronic disease. These three galaxies and the focus on the individual are important, as for example in Zambia various stressors had an impact on diabetes management [156]. These stressors included poverty, discrimination, keeping diabetes a secret, stigma, lack of family support, and worrying about the future, emphasizing the importance of wider issues that go beyond the health system in having an impact on diabetes. For diabetes and specifically for type 1 diabetes in children, there is a need to involve parents and families. This family outreach has been part and parcel of many HIV/AIDS programmes and can be seen as an area that could be important for diabetes [157].

In addressing the care of people with diabetes, there needs to be a focus on the individual. Managing a child with type 1 diabetes in a rural area of an LMIC is very different to a bank executive in the capital city with type 2 diabetes. Many of the requirements an individual will have for managing their diabetes daily have traditionally been seen as external to the health system [158], but they do have to be addressed to appropriately manage their diabetes. For this, people with diabetes need to be part of the solutions that are developed by the health system to meet their needs [88]. This requires the delivery of quality and responsive care as well as a focus on the individual. With this there is a need to have people-centred health systems [159, 160]. People-centred care involves not only focusing on the delivery of care and involving people in this, but also the governance and decision-making processes [161]. The health system should be focused and organized around people, rather than diseases. The aim is to address the needs and expectations of people and communities considering the context of people's family, community, and culture [162]. Given that the actual burden of care is on the individual in managing their condition on a daily basis outside the formal health system, this is a challenge for health professionals in the way they provide information and knowledge to the person with diabetes [163]. It requires training, allocating or defining different roles for different health professionals, a team approach to care, and a shift in the role of the health professional from being an expert and providing directives to an individual, to being a mode of support and providing guidance and recommendations to the individual as they care for their diabetes [164].

Within this framework, users of the health system are seen as active participants in the delivery of services and should have channels to actively voice their concerns, to shape health services and policies, as well as to hold health providers and policy makers accountable [165]. Beyond including the individual, there is also an active role for families and the community [9]. The WHO's Innovative Care for Chronic Conditions Framework (ICCCF), a model developed to help health systems transition from acute to chronic care and highlight the different components necessary for this, states that individuals, families, and communities are underused as resources for the health system [9]. Within the ICCCF individuals, families, and communities are seen as partners to the health system rather than recipients. That is viewed as essential, given that people with diabetes need to be active in their care to ensure proper outcomes. This role given to individuals, families, and communities not only needs to be integral to the interaction between the provider and the person with diabetes, but also engrained within the system and policy context.

In Thailand and Jamaica, different peer-led support interventions with the aim of improving diabetes knowledge have been implemented, including group meetings, education, as well as home visits [166]. Other approaches used community health workers for outreach activities. Community involvement is also an essential component of HIV/AIDS care in LMICs, with care being devolved outside the formal health system to the community and even to people's homes, with lay people trained to provide some elements of care and support [157].

Within addressing the needs of the population, two approaches could be integrated into those developed by the health system. The first is to take a needs-based approach. This has been described for type 1 diabetes [158, 167]. The focus would be laid on the more pressing needs first and a hierarchical approach taken to meeting these. For example, ensuring that insulin is available, because it is necessary for survival, could be done through different means, including universal health coverage policies and policies beyond the ministry of health, which might address the cost of insulin, supply systems, organization of care, and so on. At a later stage, once the essential survival needs are met, more complex needs around tailoring of education and fully integrating the community would be addressed.

Another approach is to involve people with diabetes in developing solutions within the health system to meet their needs, instead of these being driven by policy makers, healthcare providers, or other experts. So called co-creation or co-design approaches where the beneficiaries are directly involved in developing solutions [168] can also be a tool for involving people with diabetes in addressing the challenges they face, as has been done in HICs [169]. Involvement of communities in the organization of services

delivered by primary healthcare leads to these being of better quality, more frequently used, with increased accountability, as well as improved health outcomes [161]. In HIV/AIDS programmes developed and implemented in LMICs, people living with HIV/AIDS played an important role in supporting the health system, their peers, and advocacy-related activities [157]. Through this involvement not only were these initiatives focused on the individual, they also addressed many challenges around the stigma associated with HIV/AIDS.

How can this be achieved?

Lessons from Mozambique and Kyrgyzstan show that in order to improve the health system for diabetes certain elements are needed [8]. First, it is important to have wide-ranging legal and policy documents to address the issues of access to medicines, organization of care, human resources, and diagnostic tools. Secondly, with regard to organization of care, for type 2 diabetes both countries are trying to shift diabetes care to primary healthcare with a focus on training of health personnel. In tackling the issue of access to medicines, the role of diabetes associations, professionals, and research has assisted in documenting and then acting on the barriers present.

Human resources are a key component in addressing diabetes in LMICs. Thus, training should be integrated into the curricula of doctors and nurses in medical and nursing faculties as well as in continuing professional development [21]. This would include clear definitions of tasks, including task sharing or shifting [170], with redistribution of certain tasks from doctors to nurses as well as from specialists to primary care physicians [171]. This would allow a redistribution of the workload and would benefit from the complementary strengths of each professional in the provision of care. Task sharing is effective in other fields such as antenatal care and in HIV/AIDS and tuberculosis programmes [166]. The role of nurses and other health professionals should be fostered, with this training being based on clear, applicable, and socioeconomically contextualized guidelines [45]. In addition, the inclusion of pharmacists in interprofessional teams could also be used to improve access to care [172]; the same applied to traditional healers [20].

A recent systematic review and meta-analysis of health system interventions in LMICs aiming to improve outcomes in people with diabetes found that health system interventions for type 2 diabetes may be effective in improving glycaemic management. Multicomponent clinic-based interventions had the strongest evidence for glycaemic benefit among intervention types [32]. Other examples of health system interventions were pharmacist task sharing, diabetes education or support alone, and nursing case management interventions, among others. The WHO's Package of Essential Noncommunicable Disease Interventions (WHO-PEN) for primary care settings includes protocols for the management of major NCDs, as well as a list of diagnostic tools and medicines required at this level of the health system [14] (Box 75.2). Some lessons learnt during the Covid-19 pandemic, such as triage to select those most in need of face-to-face consultations, use of telemedicine, task sharing/shifting, decentralized distribution of medicines, and redirection to alternate facilities, could become the new normal to address current challenges in access to care [59].

In linking training with the delivery of services, there is also a need for training in the management of chronic conditions, patient education, and communication [173]. This requires not only clinical competencies, but also organizational and personal skills development. Each element of service delivery needs to be organized with the individual in mind, from the consultation to the diabetes clinic if a special clinic is part of the services provided, to the given facility as well as referrals and counter-referrals. Diabetes care needs to be incorporated into the services offered within primary care, in addition to providing general primary care services, in facilities that are safe and of good quality. Care provided covers basic chronic care including health promotion, identification and management of risks, and patient education in self-care and treatment of diabetes and comorbidities, with the possibility of referring on in case of need [174].

A key element of the delivery of care is the collection of data at different levels of the health system and for different purposes. This goes from patient data to help in the management and follow-up of an individual to facility and even subnational and national data as part of a routine surveillance system, allowing for the improvement of programmatic planning and resource management (e.g. human, medicines, laboratory), as well as helping in the planning and procurement of medicines and other supplies. For patient-related data, creation of health passports containing medical information and appointment dates might be an option to guarantee continuity of information for a given individual [22]. Research is also needed to further document the burden as well as to test adapted solutions for LMICs [6].

The final component to the delivery of care is of course access to medicines, which is especially important for type 1 diabetes, as access to insulin is vital for survival. Medicines for diabetes should be available as close as possible to the individual at an affordable price, if not for free. This requires policies to be in place around universal health coverage as well as regulation of prices and mark-ups within the health system. In parallel to medicines there is also a need to have different laboratory tools and tests available (Box 75.2), with these being adapted to the level of the health system as well as affordable to individuals.

Innovation and new technologies = new opportunities?

Technology and innovations have the potential to affect all aspects of diabetes care in LMICs, from data collection to education for individuals and possibly service delivery. LMICs need to create and implement new information technologies to take decisions based on their own evidence. However, data collection, periodic analysis,

Box 75.2 Elements of the World Health Organization Package of Essential Noncommunicable disease interventions (WHO-PEN) for diabetes.

WHO-PEN provides a comprehensive set of tools for the management and care of non-communicable diseases, including diabetes, in primary healthcare.

Diagnostic tools	Medicines
Glucometer	Insulin
Urine protein test strips	Metformin
Urine ketone test strips	Glibenclamide,
Blood cholesterol assay	Gliclazide
Lipid profile	
Serum creatinine assay	
Urine microalbuminuria test strips	
Semmes-Weinstein 10g monofilament	

Source: World Health Organization 2020 [14].

interpretation, and use have to be systematic and if possible automated [8]. The introduction of technological innovations such as digital health strategies with decision support tools [175], including patient reminders with health education messages through text messages, or automated monitoring and self-care support calls, is facilitated by mobile phones, which are easy to use and widely available, even in LMICs [22]. While access to care might be challenging in remote areas, provision of contextualized digital technology services to patients, such as text messages, improves diabetes outcomes (i.e. HbA_{1c}) and gives patients a feeling of being cared for [176]. Telehealth gained traction during Covid-19 for the management of diabetes [177] and in HICs has been used to address the shortage of healthcare specialists [178]. Electronic records are also a tool that can address a gap in the health system environment in LMICs in collecting data and in ensuring their use to improve the quality of care [179].

One area where innovation has been described is with regard to diagnostic tests, either standalone or in conjunction with other mobile devices [6]. Devices attached to mobile phones, for example for eye complication screening, are other innovations that can help improve diabetes care in LMICs. Many of these new technologies or solutions have only been piloted in LMICs, requiring further evidence as well as the feasibility of scaling up [180], for instance the use of foot thermometry and mHealth for the prevention of foot ulcers [181]. Innovation could include heat-stable insulin and self-monitoring equipment, in addition to monitoring tools adapted to LMIC contexts. Beyond innovation in new technologies, innovation in delivery of care should not be neglected [182], as well as ensuring that innovations are equitably accessible, as even though insulin was discovered 100 years ago it remains inaccessible to many.

Conclusion

The WHO defines health as total social, psychological, and physical well-being [183]. In order to achieve health for the populations they serve, health systems need to adapt their role to meet the needs of their populations. Despite having seen success in addressing a variety of health challenges for populations in LMICs, such as maternal and child health and HIV/AIDS, the responses to date for diabetes have been insufficient. This is due to the various barriers described (Table 75.1). Clearly, one issue to be addressed is funding for diabetes in order to ensure that the financial burden does not fall on the individual. For LMICs this requires both governments and donors to act together. Although there have been global calls regarding diabetes and NCDs, as of yet these have not been answered with adequate resources and approaches. Much focus has been given to addressing the increasing burden of type 2 diabetes, to the detriment of addressing the challenges within the health system. Evidently there is a need to stem the rising prevalence of type 2 diabetes, but this should both involve the health system and not avoid the complex issues around addressing access to care.

This focus on health systems and diabetes care both is an issue of equality and needs to differentiate between type 1 diabetes and type 2 diabetes. For type 1 diabetes, without access to insulin and care survival cannot be guaranteed. Given that 2021 was the centenary of insulin access, this needs to feature prominently on both global and national agendas. The approach should focus on ensuring that people who have been diagnosed with type 1 diabetes can access care in an optimal way. This would guarantee that the investment in providing care that both the health system and the individual pay for is optimized. It would also benefit people with type 1 diabetes and type 2 diabetes in laying the foundations for improved access to care.

In developing global and national health system and community responses, there is a need to understand the current situation with regard to the health system and its capacity to deliver diabetes care. Using the six health system building blocks as pillars for this response, policy makers, professionals in the health system, diabetes associations and advocates, and individuals with diabetes need to ensure that the principles of integration, continuity, universality, responsiveness, quality, and a focus on the individual are all part of the solutions proposed to address this complex issue (Table 75.2).

All these components will be needed for better use of resources to guarantee access to diabetes care for all, including vulnerable populations. Diabetes in LMICs is a global health problem that can no longer be ignored and will require global, national, health system, community, and individual responses. All these responses

Table 75.2 Overview of solutions.

Healthcare workforce	Information	Medical products	Service delivery	Financing	Leadership and governance
		Integration			
Optimally use human resources: nurses, community health workers, pharmacists, traditional healers	New technologies Data for programmatic planning, routine surveillance, and resource management Registers	Role of pharmacists Point-of-care devices available at different levels of care Bundling	Packages of services beyond diabetes	Public and private sources of funding Strengthening primary healthcare Removal of different tariffs and taxes on medicines Collaboration between ministry of health and other government sectors Taxes on sugar-sweetened beverages as a means of resource generation	Multisectoral approaches Strengthening primary healthcare and health system's role in prevention and beyond the health sector

(*continued*)

Table 75.2 (*Continued*)

Healthcare workforce	Information	Medical products	Service delivery	Financing	Leadership and governance
		Continuity of care			
Training in chronic disease management Task sharing	Data follow the individual and are available where care is provided	Ensure continuous access and affordability	Models of care guarantee continuity of care across diseases and levels of the health system	Financial coverage from prevention to treatment rehabilitation and palliative care, with a specific focus on primary healthcare	Focus on primary healthcare, defining complications covered by universal health coverage
		Universality			
Healthcare workers sensitized to issues of universality	Health system data assist in guaranteeing universal access	Equitable access	Non-discriminatory health system Decentralization	Financial protection from the costs of care	Universal health coverage features prominently on the agenda
		Quality and responsiveness			
Training in provision of care Training in organization of care Training in management of primary healthcare Supportive supervision	Data collection allows for monitoring of quality and responsiveness Digital support tools for decision making	Prequalification, essential medicines, and technologies	Implementation of chronic care services with referral mechanisms Audit of services	Performance-based payments	Accountability measures for the health system and providers Better primary healthcare management
Focus on the individual Training in communication skills Training in patient education	Data follow the individual Digital support tools	Self-management and control Simplified guidelines/ modes of delivery/storage User-friendly, adapted, and thermostable medicines and devices	Tailoring of services to meet the individual's needs	Health insurance schemes covering care for non-communicable diseases	Accountability to the individual Involvement of individuals, families, and communities in defining priorities and models of care

should actively involve individuals with diabetes in order to ensure that the strategies developed address specific challenges that are context and person specific. Margaret Chan, the former Director-General of the WHO, stated in 2011: 'Building a health system takes time, and improvements are difficult to measure. But this is the one area where investments are most desperately needed. . . . Health systems are social institutions. They do far more for society than deliver babies and pills, like a post office delivering parcels. Properly managed and adequately financed, a fair and equitable health system contributes to social cohesion and stability' [184]. Therefore, for the reality of diabetes to fundamentally change in LMICs, health systems need to be at the centre of the response.

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13 Future Directions

76 Immunotherapies for Type 1 Diabetes

Jesper Johannesen[1,2,3] and Flemming Pociot[2,3]

[1] Department of Paediatrics and Adolescent Medicine, Herlev and Gentofte Hospital, Copenhagen, Denmark
[2] Steno Diabetes Center Copenhagen, Copenhagen, Denmark
[3] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Key points

- Type 1 diabetes is a chronic immune-mediated disease causing death of the insulin-producing pancreatic β cells. The progressive loss of β cells is mainly caused by autoimmune inflammation.
- An even deeper understanding of the immunopathological processes of type 1 diabetes is needed to tailor innovative and more efficient immunotherapies.
- One of the major obstacles to success is that increasing data suggest that type 1 diabetes is a heterogeneous disease.
- Current preventive immunomodulating therapies close to the clinical onset of type 1 diabetes seem, at best, to induce a temporary effect, with the long-term outcome being less satisfactory.
- Not all participants in the preventive type 1 diabetes trials conducted so far have benefited from the tested intervention. New strategies are warranted to identify responders versus non-responders and the development of better biomarkers.
- The timing of the immunotherapy in relation to the different stages of type 1 diabetes progression needs further exploration.
- Immunotherapy, as combination treatment designed to interact with different targets involved in the type 1 diabetes pathogenesis, has potential advantages over monotherapy: it allows lower doses of *riskier* agents, and has fewer side effects, as seen within other complex diseases.

Type 1 diabetes is a chronic immune-mediated disease, causing attrition and death of the insulin-producing pancreatic β cells, resulting in a life-long requirement for exogenous insulin. The progressive loss of β cells is mainly caused by autoimmune inflammation. The aetiology and pathological mechanisms remain to be completely understood. Type 1 diabetes has a strong genetic component, where contributions from several genes influence disease development [1]. In addition to genetic predisposition, environmental and epigenetic factors influence disease susceptibility [2, 3]. Worldwide more than 20 million people are afflicted with type 1 diabetes and in most countries type 1 diabetes incidence is increasing by 3–4% every year, most notably in children and adolescents [4]. This globally rising incidence of type 1 diabetes calls for effective preventive measures. The main obstacles to the successful prevention of type 1 diabetes are:

- Incomplete understanding of the disease pathogenesis.
- Heterogeneity of type 1 diabetes.
- Lack of biomarkers for cost-effective screening of first-degree type 1 diabetes relatives and within the general population.

The dilemma is that in the early stages of the disease process more effective interventions may be used, but the disease prediction is poorer, and a larger population is predisposed to potential side effects of the treatment. In contrast, in later stages the disease prediction is more precise, but applicable interventions are less effective due to the already advanced disease process.

The presence of genetic polymorphisms of human leucocyte antigen (HLA) complex and multiple autoantibodies, which appear early in life, are highly predictive of type 1 diabetes [5]. Currently, best-practice genetic screening for HLA risk haplotypes identifies individuals at risk of type 1 diabetes and the presence of autoantibodies informs its progression.

Despite modern treatment regimens that increasingly embrace advanced technology [6], mortality in people type 1 diabetes with excellent glycaemic indices (glycated haemoglobin [HbA_{1c}] <6.9%; 52 mmol/mol) is still twice that of matched individuals without diabetes, increasing to more than eight times higher risk in severely dysregulated type 1 diabetes [7]. Hence, there is an urgent need to explore disease-modifying strategies [8].

Type 1 diabetes as an autoimmune disease

As described in depth in Chapter 14, the β-cell autoimmunity in type 1 diabetes is characterized by an inflammatory response with a progressive infiltration of several immune cells within the pancreatic islet [9]. This disease process typically begins years prior to the presentation of overt type 1 diabetes [10]. The immune cells involved in the process are $CD4^+$, $CD8^+$ positive T cells, macrophages, dendritic cells, and B cells [8]. However, a reported lack of T-cell infiltrates in human pancreata implicates the heterogeneous nature of the immunopathology [11]. This is supported clinically by the rapid and severe type 1 diabetes development in children and adolescents [12], with a broader and more aggressive

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β-cell–specific T-cell response as opposed to the development of type 1 diabetes in adults [13, 14]. There is an imbalance between the T-regulator (Treg) cells and T-effector cells [15], as well as dysregulation of the antigen-presenting cells [16], exhibiting proinflammatory properties driving a skewed differentiation of naïve T cells towards pathogenic T-effector cells, as well as directly being part of the islet inflammation and β-cell destruction by interleukin-1 (IL-1), tumour necrosis factor-α (TNF-α), and interferon γ (IFNγ) production [17, 18]. Type 1 diabetes autoantibodies against multiple targets include insulin (IAA), glutamate decarboxylase (GAD), islet antigen 2 (IA-2), and the zinc transporter 8 (ZnT8); these are merely disease markers and do not damage the β cells [19]. Notably, the CD4 and CD8 T cells recognize the same epitopes. Furthermore, there seems to be a critical role of the β cells functioning as antigen-presenting cells [19, 20], especially as part of the cellular infiltrate before the age of 7 years [21]. Finally, the contribution of the β cell itself in type 1 diabetes seems to be complex, as the β cells are involved by the upregulation of HLA, self-antigen presentation, and secretion of chemoattractant molecules attracting and focusing T cells with a cytotoxic potential [18, 22]. This leads to β-cell damage, probably giving rise to post-transcriptional or post-translational modified islet proteins acting as strong triggers of T-cell activation [23], giving the islet infiltrate and β-cell damage further momentum; hence the β cell seems to interact with the immune system in an unfavourable way.

Definition of the natural history, staging, and how to evaluate disease progression by different biomarkers

Genetic characterization in terms of genome-wide association studies can be used to identify individuals at risk of developing type 1 diabetes, where the HLA system (in particular DR-DQ) is attributed to approximately half the genetic risk [1]. A combination of HLA and non-HLA gene polymorphisms in polygenic risk scores improves prediction, and it has been estimated that 77% of future cases could be identified by following 9.6% of screened children [24]. Using this approach, population-based screening identifies newborns with ~10% risk of developing autoimmunity before the age of 6 years.

Type 1 diabetes is the common endpoint of T cell–mediated destruction of pancreatic β cells, but the variability in clinical phenotype and pre- and post-onset rate of β-cell decline suggests the presence of multiple underlying pathways. Age is a strong but imperfect predictor of C-peptide decline [21]. Variability in β-cell decline mandates longer and larger clinical trials to power the most common primary outcome measure of stimulated C-peptide area under the curve (AUC). Early identification of *rapid progressors* would permit shorter studies with fewer participants and reduce the risk-to-benefit ratio.

Finally, there is increasing recognition of distinct endo-types in those with recent-onset type 1 diabetes, reflective of varied pathobiology. Improved understanding of these endo-types and the development of relevant biomarkers will permit targeted therapeutic interventions [14, 25].

The pre-clinical phase of type 1 diabetes is divided into two distinct stages:

- Stage 1: defined as β-cell autoimmunity with two or more positive islet autoantibodies with normal glucose metabolism.
- Stage 2: characterized by autoantibody positivity and glucose intolerance.

Stage 3 (phase two) defines the clinical diagnosis with clinical manifestations of type 1 diabetes [26] (Figure 76.1). This staging may pave the way for better-targeted intervention strategies. As demonstrated within The Environmental Determinants of Diabetes in the Young (TEDDY) and the Finnish Diabetes Prediction and Prevention (DIPP) studies, a clear relationship exists between the number of positive autoantibodies and the risk of later clinical type 1 diabetes, with a five-year risk of progression to overt type 1 diabetes of 11%, 36%, and 47% in individuals with one, two, or three autoantibodies, respectively [27]. At stage 3 more than 90% are positive for at least one autoantibody against either IAA, GAD, IA-2, or ZnT8 [28].

Beyond genetics and autoantibody positivity, T-cell biomarkers have the potential to characterize the underlying pre-type 1 diabetes progression, onset, and response to intervention initiatives [29]. A better understanding of the T-cell receptor repertoire of the pathogenic T cells has the potential to serve as a surrogate marker reflecting the efficacy of forthcoming immunotherapy interventions.

The β cells themselves may have an important role in driving the autoimmune process leading to clinical type 1 diabetes. As described earlier, a complex interaction takes place between the β cells and the immune system during the pathogenic processes [23, 30, 31]. As a cell type with a high biosynthesis rate, the β cell seems especially vulnerable to stress-induced changes during inflammatory events and altered β-cell physiology has been noted once the autoimmune process is ongoing, which might accelerate β-cell killing [32]. Furthermore, immune-histopathological human studies demonstrate a disconnection between β-cell function and β-cell mass in the pancreas of humans with type 1 diabetes. Despite a severe decrease in C-peptide production, insulin-positive cells can still be identified in significant numbers in many individuals with type 1 diabetes in the years following diagnosis [33, 34]. Hence, all the β cells may not be destroyed; instead, the remaining β cells might be dysfunctional [35], and the balance between β-cell loss and β-cell dysfunction could be individual.

Prevention of type 1 diabetes

The prevention of type 1 diabetes can be divided into four stages (Figure 76.1):

1. Primary prevention before the onset of islet autoimmunity.
2. Secondary prevention before the diagnosis of type 1 diabetes.
3. Tertiary prevention in individuals with newly diagnosed type 1 diabetes to preserve residual β-cell function.
4. Late prevention of secondary complications in established type 1 diabetes and attempts to revive lost β-cell function.

The vision is to discover a primary prevention approach safe enough to be administered to the general childhood population without the evaluation of disease risk [26]. A lead candidate for such a measure would be a preventive vaccine for early immunization [36]. To date, prevention trials carried out in human populations have demonstrated only limited success in achieving their goal [37]. Some past and ongoing trials are summarized in Table 76.1. The most promising results have been achieved in studies of teplizumab [49], rituximab [54], alefacept [59], abatacept [60], and anti-thymocyte globulin [57]. A transient benefit after the administration of oral insulin was seen in a subgroup of individuals with high IAA levels in the Diabetes Prevention Trial-Type 1 [61], details of which are given later.

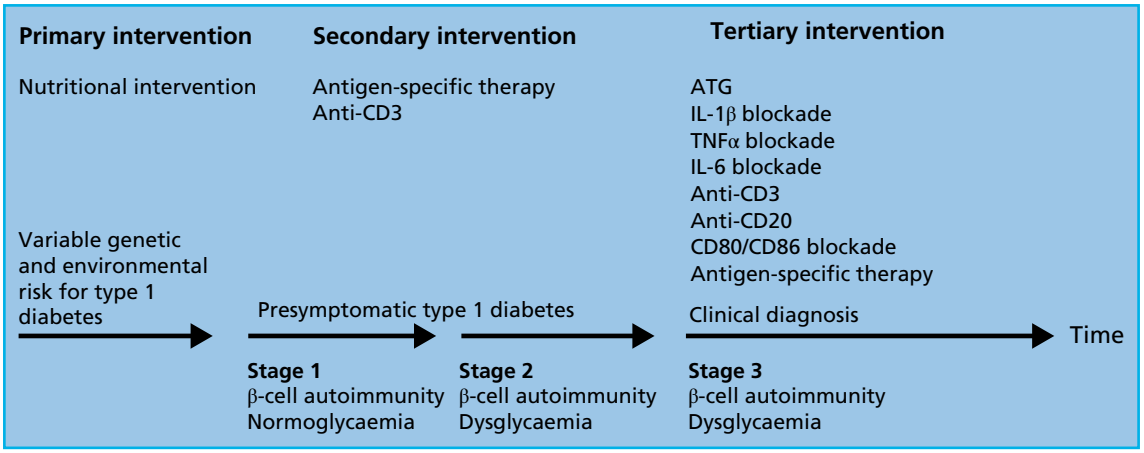

Figure 76.1 Stages of type 1 diabetes, with corresponding interventions and intervention approaches. Type 1 diabetes is a continuum that begins prior to symptomatic disease with well-defined, reproducible early stages. Stages 1 and 2 are defined by the presence of multiple autoantibodies. Different intervention strategies apply to these stages. Examples of immune therapy approaches used at the different stages are shown. ATG, anti-thymocyte globulin; IL, interleukin; TNF-α, tumour necrosis factor α.

Table 76.1 Some previous and ongoing trials aimed at preventing type 1 diabetes.

Study	Intervention	Stage	Outcome achieved	Reference/ClinicalTrials.gov identifier
TRIGR	Hydrolysed casein formula	Primary	No	[38]
BABYDIET	Gluten-free diet during first year	Primary	No	[39]
Pre-POINT	Oral/intranasal insulin	Primary	Yes (immune response to insulin)	[40]
DIPP	Intranasal insulin	Secondary	No	[41]
DPT-1	Oral insulin	Secondary	Transient benefit in subgroup with high IAA levels	[42]
DPT-1	Parenteral insulin	Secondary	No	[43]
Belgian Diabetes Registry	Subcutaneous insulin	Secondary	No	[44]
TrialNet	Oral insulin	Secondary	No	[45]
INIT-II	Intranasal insulin	Secondary	Ongoing – rate of new diabetes	NCT00336674
ENDIT	Nicotinamide (vitamin B_3)	Secondary	No	[46]
DENIS	Nicotinamide	Secondary	No	[47]
DIAPREV-IT	Alum-GAD	Secondary	No	[48]
DIAPREV-IT2	Alum-GAD + vitamin D_3 2000 IU/d	Secondary	Ongoing – rate of new diabetes	NCT02387164
TrialNet	Teplizumab	Secondary	Yes – rate of new diabetes	[49]
TrialNet	Teplizumab	Tertiary	Yes	[50]
TrialNet	Abatacept	Tertiary	Yes – Stimulated C-peptide at the 2-yr visit	[51]
TrialNet, AIDA	Canakinumab, anakinra	Tertiary	No	[52]
TrialNet	GAD vaccine	Tertiary	No	[8]
TrialNet	Mycophenolate mofetil/daclizumab	Tertiary	No	[53]
TrialNet	Rituximab	Tertiary	No long-term effect	[54]
DEFEND-1	Otelixizumab	Tertiary	No	[55]
T1DAL	Alefacept	Tertiary	Yes – stimulated C-peptide	[56]
TrialNet	Anti-thymocyte globulin	Tertiary	Yes – stimulated C-peptide at 1- and 2-yr visits	[57]
T1GER	Golimumab	Tertiary	Yes – stimulated C-peptide at 1-yr visit	[58]

GAD, glutamate decarboxylase; IAA, insulin.

Immunotherapy approaches

The first proof-of-concept studies indicating that immunotherapy could be a way of preserving β-cell function came from the use of cyclosporine in new-onset type 1 diabetes, which was first tested in the 1980s [62, 63] and successfully prolonged the remission phase. However, due to severe side effects, mainly nephrotoxicity, the use of cyclosporine ceased. Later on anti-lymphocyte globulin and small molecules (cyclosporine, azathioprine, and glucocorticoids) were commonly used in a regimen as a means of non-specific immunosuppression for β-cell preservation in individuals with type 1 diabetes or in islet transplantation [64]. While glucocorticoids are widely used as an immunosuppressive steroid to treat autoimmunity [65], it is

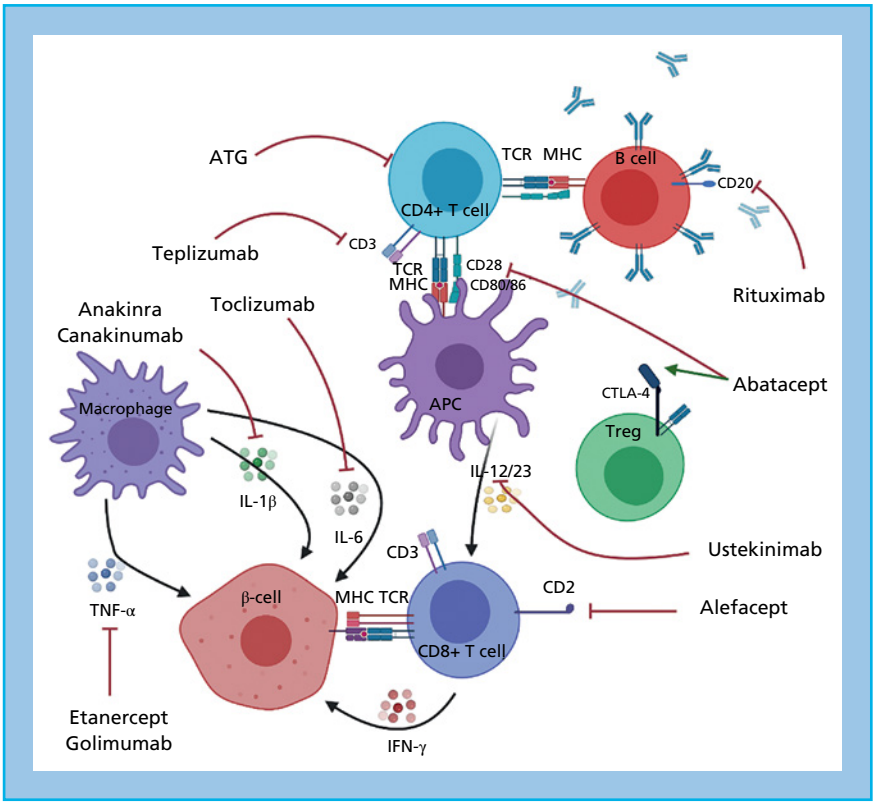

Figure 76.2 Mechanisms of immunotherapy in type 1 diabetes. A simplified model of the pathogenesis of type 1 diabetes showing the β cell and immune cells with the targets of different immunotherapies. Immune therapy targets are shown on one cell only despite the targeted receptor, e.g. CD3, potentially being expressed on several cell types. ATG, anti-thymocyte globulin; IL, interleukin; MHC, major histocompatibility complex; TCR, T-cell receptor; TNF-α, tumour necrosis factor α.

increasingly clear that glucocorticoids adversely stimulate gluconeogenesis in the liver and antagonize the insulin-mediated uptake of glucose [66]. The induction of peripheral insulin resistance is counterproductive to the desired effect of β-cell preservation. A major improvement in immune suppression treatment was introduced with the Edmonton protocol, which used a glucocorticoid-free regimen comprising sirolimus, tacrolimus, and daclizumab [67].

Today most immunotherapies in type 1 diabetes are based on the known pathogenetic mechanisms underlying the development of the disease (Figure 76.2). These targeted therapies and their outcome at various stages of type 1 diabetes development are detailed in what follows. They can broadly be divided into non-antigen or antigen-specific intervention strategies, the former including T-cell and B-cell as well anti-cytokine targeting modalities.

Targeting T cells

CD3 blockade (teplizumab and otelixizumab)

Mode of action

Teplizumab and otelixizumab are non-activating, Fc-modified, anti-CD3 monoclonal antibodies thought to attenuate activated autoreactive T cells. Such T cells disappear from the peripheral circulation during immunotherapy, but return within weeks after the end of treatment. Pre-clinical and clinical studies in type 1 diabetes suggest that the drug may induce Treg activity, indicating augmented immune tolerance. Hagopian et al. demonstrated that the effect of the anti-CD3 monoclonal antibody seems to be mediated by transient reduction in the $CD4^+$ and $CD8^+$ cells during the cycle of treatment. Both may be relevant mechanisms of action of teplizumab, wherein the T-effector cells, which are maintaining an inflammatory environment in the pancreas, are preferentially depleted while Tregs are favoured [68]. Later, expansion of $CD8^+$ Tregs and $CD8^+$ T-effector cells exhibiting an exhausted phenotype has been reported [69].

Pre-diabetes studies

The use of teplizumab in TrialNet (TN-10) in first-degree relatives of individuals with type 1 diabetes was the first trial to meet its clinical endpoint of delaying the onset of type 1 diabetes [49]. At the end of the trial, 25 of the 44 participants in the intervention group (57%) were diabetes free. The longest follow-up was >5 years (88 months). The annual incidence rates of type 1 diabetes were 14.9% and 35.9% in the teplizumab versus placebo groups, respectively ($p = 0.006$). The two-year delay in diagnosis is clinically important, as any time without clinical diabetes has significance, particularly for children, who were ~70% of the study participants ($n = 76$ in total). Notably, biomarkers identified those participants most likely to respond to the treatment. Repeated dosing, or combinations of teplizumab with other agents with complementary mechanisms of action likely to increase the ability to delay or prevent the progression of clinical disease, are warranted in the future. In November 2022, the FDA approved teplizumab injection to delay the onset of stage 3 type 1 diabetes in adults and children aged 8 years and older who currently have stage 2 type 1 diabetes.

New-onset studies

Anti-CD3 treatment has been tested in individuals with newly diagnosed type 1 diabetes in various formulations (teplizumab and otelixizumab), designs (one or multiple administrations), and doses. Generally, a greater β-cell preservation with a slower decline in C-peptide over time was demonstrated; however, dose dependency in relation to C-peptide preservation and adverse effects seems to exist. A recent meta-analysis including eight randomized

trials comprising 866 participants demonstrated a higher value of C-peptide AUC at 24 months, but no difference in HbA_{1c} could be demonstrated at any time point (onset to 24 months) between the teplizumab group versus placebo [70].

In a study by Keymeulen testing 48 mg otelixizumab in 80 randomized individuals with type 1 diabetes aged 12–39 years, higher C-peptide release at 18 months was demonstrated in the intervention group versus placebo, but no difference in HbA_{1c} between the groups was seen [71]. In a four-year follow-up study, lower exogenous insulin doses were observed within the intervention group, with higher C-peptide response to a glucose clamp among the youngest age groups within the otelixizumab-treated individuals [72]. The dose of 3.1 mg otelixizumab has also been tested in the Durable-response therapy Evaluation For Early- or New-onset type 1 Diabetes (DEFEND-1 and DEFEND-2) studies, but C-peptide preservation was not demonstrated [55, 73]. A recent randomized, single-blind, placebo-controlled, 24-month, dose–response study (16–27 years old, <32 days from diagnosis of type 1 diabetes) using otelixizumab (cumulative intravenous [IV] dose 9, 18, or 27 mg over 6 d) demonstrated that the adverse effects were dose dependent and only the dose of 9 mg otelixizumab led to a change from baseline mixed-meal tolerance test C-peptide weighted mean AUC at 18 months (difference from placebo 0.39; p = 0.023); no β-cell function preservation was seen with otelixizumab 18 and 27 mg [74].

The other CD3 blocking agent, teplizumab, was tested in a two-course administration design (Autoimmunity-blocking Antibody for TolErance in recently diagnosed type 1 diabetes [AbATE] study; cumulative dose 11.6 mg and 12.4 mg at baseline and after one year) comprising 52 actively treated versus 25 placebo individuals with newly diagnosed type 1 diabetes (aged 8–30 years), with the first dose being given within eight weeks post-diagnosis. At 24 months the baseline (at entry) adjusted mean C-peptide AUC levels were 75% higher in the intervention group versus control; however, no difference in HbA_{1c} between the groups was demonstrated at 24-month follow-up. Within the group defined as responders (45% of the total intervention group who had lost less C-peptide than the control group), lower HbA_{1c} at entry of the study was demonstrated [50]. These findings were confirmed within the Protégé study comprising >500 participants [68]. The one-year responders from the 2013 Herold et al. study maintained a higher C-peptide at the seven-year follow-up compared to the placebo group, still without any difference in HbA_{1c} [75].

Safety

Adverse drug-related events were transient and resolved spontaneously. Fever, nausea, vomiting, rash, and headaches as well as mild forms of cytokine release syndrome were observed, and transient increases in the viral load of cytomegalovirus (CMV) and Epstein–Barr virus (EBV) were measured in drug-treated participants who were seropositive at study entry. Mild transient cytopaenia and small increases in transaminases were also seen.

CD2 blockade (alefacept)

Mode of action

Alefacept (LFA3-Ig) is a dimeric fusion protein that was the first biological US Food and Drug Administration (FDA)-approved drug for moderate to severe plaque psoriasis [76]. It comprises two LFA-3 molecules bound to the Fc portion of immunoglobulin (Ig) G1 that binds CD2, which is expressed most prominently on $CD4^+$ and $CD8^+$ effector memory T cells (Tem cells), the cells thought to be primarily responsible for β-cell destruction in type 1 diabetes. In the Rigby study, alefacept was associated with an increase in the Treg/CD4+ Tem and Treg/CD8+ Tem ratios, possibly leading to a higher ratio of Tregs to cytotoxic T cells. The effect of alefacept may be mediated by an increased expression of the programmed death-1 (PD-1) receptor demonstrated in the $CD4^+$ cells, mediating downregulation of its effector functions [59].

Pre-diabetes studies

None.

New-onset studies

The Inducing remission in Type 1 Diabetes with ALefacept (T1DAL) study is a phase II, double-blind, placebo-controlled trial that randomized individuals with newly diagnosed type 1 diabetes, aged 12–35 years, to alefacept (n = 33; two 12-wk courses of 15 mg intramuscularly [IM]/wk, separated by a 12-wk pause) or to placebo (n = 16). The primary outcome of higher change from baseline 2 h C-peptide AUC during a mixed-meal tolerance test was not met when comparing the intervention group to the control group (delta 2 h AUC: +0.015 nmol/l vs –0.115 nmol/l [p = 0.065] intervention vs placebo), despite the mean 4 h C-peptide AUC being higher (delta 4 h AUC: +0.015 nmol/l vs –0.156 nmol/l [p = 0.019] intervention vs placebo) and lower insulin requirements being reported. There was no difference in HbA_{1c} at 12 months (6.9% vs 7.2%; 52 mmol/mol vs 55 mmol/mol [p = 0.75] alefacept vs placebo, respectively) [56]. At the 24-month follow-up, both the 2 h and 4 h C-peptide AUC demonstrated higher C-peptide production within the alefacept-treated group compared to placebo (delta 2 h AUC: –0.185 nmol/l vs –0.334 nmol/l [p = 0.015] intervention vs placebo; delta 4 h AUC: –0.134 nmol/l vs –0.368 nmol/l [p = 0.002] intervention vs placebo). Furthermore, exogenous insulin need and prevalence of severe hypoglycaemic episodes were markedly reduced; however, no difference in HbA_{1c} was observed (7.4–7.5%) (57–58 mmol/mol in both groups) [59]. A *post hoc* analysis demonstrated a strong inverse association between the 4 h C-peptide AUC and risk of severe hypoglycaemia, glucose variability, and insulin dose–adjusted HbA_{1C} values, with no difference between the alefacept treated and placebo, suggesting that natural variability as well as immune intervention with alefacept-induced preserved β-cell function benefits the person with new-onset type 1 diabetes [77].

Safety

Although this trial was too small to detect uncommon adverse events, alefacept has been widely used in psoriasis for many years with a strong safety record; it does not blunt immune responses to novel and recall antigens and does not increase susceptibility to infectious disease or malignancy [59].

CD80 and CD86 blockade (abatecept, CTLA4-Ig)

Mode of action

For the full activation of T cells from an antigen-presenting cell, two signals are required. The first signal results from the interaction between the T-cell receptor and an antigen peptide presented on a major histocompatibility complex (MHC) by an antigen-presenting cell. The second and most crucial signal for the full activation of the T cell comes from the interaction between the T-cell receptor and specific ligands on the antigen-presenting cells. These ligands are CD80 and CD86, which are found on

antigen-presenting cells, and CD28 located on the surface of the T cell. This interaction results in a strong co-stimulatory signal required for the full activation of the T cell. T-cell activation can be inhibited by binding of the CD80/CD86 of the antigen-presenting cell to the CTLA4 ligand on the T cell. Hence, a therapeutic strategy to hinder autoimmunity was proposed by inhibiting the second signal to block the stimulation of the T cell by saturating the CD80/CD86 receptor of the T cells with soluble CTLA4-Ig [78]. It is speculated that the effect of abatacept relates to a decline in T-cell activation over time of at least of the initial activated T cells, alone or in combination with later components of the type 1 diabetes disease process, that might interfere with or use alternative means of T-cell activation.

Pre-diabetes studies

TrialNet is currently conducting a trial testing abatecept in type 1 diabetes, stage 1 (NCT01773707).

New-onset studies

In 2011 in a multicentre, double-masked, randomized controlled trial, Orban et al. demonstrated higher C-peptide levels in 77 abatacept-treated individuals with newly diagnosed type 1 diabetes (aged 6–36 years) than in 35 people receiving placebo. Abatacept (10 mg/kg, maximum 1000 mg/dose) or placebo was administered by IV infusion on days 1, 14, 28, and monthly thereafter for a total of 27 infusions over two years. The primary outcome was baseline-adjusted mean 2 h AUC for serum C-peptide during a mixed-meal tolerance test after two years' treatment. The adjusted C-peptide AUC was 59% higher at two years in the abatacept group (0.378 nmol/l) versus placebo (0.238 nmol/l) ($p = 0.003$). This difference was present throughout the study period, with an estimated 9.6 months' delay in decline in the abatacept treatment arm. Furthermore, at the 24-month assessment, 34 (47%) abatacept-treated individuals had HbA_{1c} <7% (53 mmol/mol), compared to 8 (26%) placebo participants ($p < 0.002$), although the exogenous insulin requirement was similar [60]. A follow-up study one year post-treatment (36 months) demonstrated a sustained C-peptide decline from a baseline of 9.5 months within the abatacept arm in parallel to the placebo group, and the HbA_{1c} also remained lower in the abatacept group (7.6%; 60 mmol/mol) versus placebo (8.6%; 70 mmol/mol) ($p < 0.005$) [51].

Safety

A few, clinically insignificant infusion-related adverse events and minimal overall adverse events were reported. A more detailed description of adverse events has been documented from the use of abatacept tested in other diseases such as rheumatic arthritis [78, 79].

Low-dose anti-thymocyte globulin

Mode of action

The efficacy of anti-thymocyte globulin (ATG) relies on its capacity to deplete lymphocytes and it has been used successfully in preventing graft-versus-host disease and suppressing allograft rejection [80]. An explanation of why higher doses of ATG (6.5 mg/kg) in monotherapy did not preserve C-peptide in new-onset type 1 diabetes has not been fully elucidated; however, flow cytometry demonstrated a significant reduction of the CD4 : CD8 ratio, and while absolute numbers of Tregs decreased, increases in Treg : Tconv (conventional T cell) ratios were observed in low-dose ATG. In contrast, flow cytometry data from a previous trial using higher-dose ATG (6.5 mg/kg) in people with new-onset type 1 diabetes demonstrated marked reductions in Treg : Tconv ratios [81, 82].

Pre-diabetes studies

None.

New-onset studies

ATG was a part of early protocols using autologous non-myeloablative haematopoietic stem cell transplantation in people with newly diagnosed type 1 diabetes [83]. ATG has also been tested in combination with prednisolone in a pilot study by Eisenbarth [84] and, more recently, retested in 38 and 20 adults with newly diagnosed type 1 diabetes receiving 6.5 mg ATG versus placebo, respectively. Neither primary endpoint of baseline-adjusted change in 2 h C-peptide AUC during a mixed-meal tolerance test from baseline to 12 and 24 months, respectively, was reached in an intention-to-treat analysis [81, 82]. In a different setting, ATG was tested at low dose in combination with pegylated granulocyte colony-stimulating factor (GCSF) in a randomized design comprising 25 individuals, mean age 23 years, on average 12 months after the diagnosis of type 1 diabetes (duration of type 1 diabetes >4 mo and <2 yr) [85, 86]. The intervention group (n = 17) received low-dose ATG 2.5 mg/kg IV followed by GCSF (6 mg subcutaneously [SC] every 2 wk for 6 doses) and eight participants received placebo. The primary outcome was the one-year change in AUC C-peptide following a 2 h mixed-meal tolerance test. Combination ATG/GCSF treatment tended to preserve β-cell function in individuals with established type 1 diabetes. The mean difference in the stimulated AUC C-peptide between treated and placebo participants was 0.28 nmol/l/min at 12 months, and HbA_{1c} was lower in those treated with ATG/GCSF at the six-month study visit.

Finally, the ATG/GCSF therapy was associated with relative preservation of Tregs. In a follow-up study, Haller et al. tested the same protocol in individuals with newly diagnosed type 1 diabetes, average age 17 years (range 12–42 years), comparing low-dose ATG/GCSF versus low-dose ATG alone and placebo in a three-arm, randomized, double-masked, placebo-controlled trial in 89 participants. There were 29 participants randomized to ATG (2.5 mg/kg IV) followed by pegylated GCSF (6 mg SC every 2 wk for 6 doses), 29 to ATG alone (2.5 mg/kg), and 31 to placebo. Low-dose ATG alone slowed the decline of C-peptide (AUC C-peptide ATG 0.646 nmol/l/min vs placebo 0.406 nmol/l/min) and reduced HbA_{1c}, whereas no difference could be demonstrated comparing ATG/GCSF (0.528 nmol/l/min) versus placebo [87]. This effect was sustained after 24 months, where lower HbA_{1c} was also observed in participants treated with ATG and ATG/GCSF.

Safety

Adverse events with ATG are an issue; in particular, cytokine release at infusion and serum sickness during the following two weeks are reported in approximately 70–80% of cases [87]. Within the low-dose ATG studies, no participants required extended hospitalization or readmission due to cytokine release or serum sickness. There were no reported cases of grade 4 or 5 adverse events (life threatening or death). In addition, no participants who received ATG/GCSF or ATG alone developed serious infections. Furthermore, between the first- and second-year endpoints, there were no increases in adverse events in ATG- or ATG/GCSF-treated participants. There were nearly twice as many adverse events reported in the placebo group than in either the

ATG or the ATG/GCSF group between the first- and second-year endpoints. No cases of EBV reactivation or severe hypoglycaemia were reported [57].

Targeting B cells

CD20 blockade (rituximab)

Mode of action

Rituximab is an anti-CD20 monoclonal antibody [88]. Because pancreatic β-cell destruction has been traditionally considered to be T cell mediated, many interventions have targeted the T-cell response. However, a role for B lymphocytes in accelerating the autoimmune β-cell destruction by T cells has also been demonstrated. In humans, increased B-lymphocyte infiltration of islets corresponds with more aggressive and earlier disease onset. B-lymphocyte depletion through a short course of an anti-CD20 monoclonal antibody temporarily preserved β-cell function in individuals with recent type 1 diabetes onset, solidifying a role for B lymphocytes in human type 1 diabetes. Orchestration of a successful autoimmune attack requires T–B cell cross-talk, and disruption of this cross-talk between antigen-specific B and T lymphocytes remains an unrealized therapeutic goal [89].

The mode of action of rituximab in type 1 diabetes is unknown. It has been proposed that rituximab reduces the production of cytokines that augment the immune response locally within the pancreas or the peripancreatic lymph nodes. It has also been suggested that the antigen presentation provided by B lymphocytes, which is required for continued T-lymphocyte action, is altered by rituximab [54].

Pre-diabetes studies

None.

New-onset studies

The Type 1 Diabetes TrialNet Anti CD-20 Study Group has orchestrated a randomized, double-blind study comprising 87 individuals with newly diagnosed type 1 diabetes (aged 8–40 years), who were assigned to receive infusions of rituximab (375 mg/m^2 body surface area [BSA]) or placebo on days 1, 8, 15, and 22, no more than three months post-diagnosis. At one-year follow-up, the primary goal was achieved of higher baseline-adjusted 2 h C-peptide AUC during a mixed-meal tolerance test for the rituximab arm (0.56 nmol/l) versus placebo (0.47 nmol/l; $p = 0.03$). Lower HbA_{1c} (rituximab 6.8% [51 mmol/mol] vs placebo 7.0% [53 mmol/mol]; $p < 0.001$) and lower exogenous insulin use (rituximab 0.39 IU/kg vs placebo 0.48 IU; $p < 0.001$) were also demonstrated in the intervention group [54]. At the two-year follow-up, the baseline-adjusted 2 h C-peptide AUC during a mixed-meal tolerance test was still higher for the rituximab versus placebo; however, the difference was no longer significant and no differences in HbA_{1c} and insulin dose were seen [90]. The B lymphocytes recovered to baseline levels at 18 months within the rituximab-treated participants.

Safety

Rituximab is considered safe in type 1 diabetes with mostly grade 1 and 2 adverse events reported (mild and moderate), and no grade 4 (life threatening). Unsurprisingly, the IgM levels were lower within the rituximab-treated individuals, an effect that persisted at 24 months, whereas the IgG levels did not differ significantly between the two groups. Increased rates of neutropaenia and infection were not seen [54, 90].

Summary of studies targeting T and B cells

The main philosophy of the studies discussed has been that the remaining β-cell capacity at onset of type 1 diabetes provides a window of opportunity to preserve the endogenous insulin production and to extend the remission phase, as individuals having a long remission phase as part of the natural history experience less severe hypoglycaemia and fewer long-term complications [91]. Most studies include a mixed population of adolescents, young adults, and adults, which potentially may harbour a bias, as increasing evidence points towards heterogeneity within the type 1 diabetes pathogenic process, especially when adjusting for age [8].

Taken together, the studies targeting immune T- or B-cell function seem to demonstrate a delay of 8–9 months in loss of C-peptide production; however, the rate of decline seems to be unaffected. Recently, Jacobsen et al. compared the latest results of teplizumab, alefacept, abatacept, high-dose ATG, low-dose ATG, low-dose ATG/GCSF, and rituximab trials in an attempt to rank the effectiveness of the agents [92]. The baseline-adjusted 2 h C-peptide AUC was modelled using analysis of covariance. Percentage increases in C-peptide over placebo and absolute within-study difference were calculated for each study for inter-study comparison. Ranking the 2h C-peptide AUC by (i) *percentage change relative to control* at one- and two-year follow-up were high-dose ATG (9% and 16%), rituximab (18% and 15%), alefacept (18% and 36%), abatacept (22% and 37%), low-dose ATG/G-CSF (30% and 49%), teplizumab (48% and 63%), and low-dose ATG (55% and 103%); and (ii) *absolute difference* presented as a point estimate for years 1 and 2 was slightly different: high-dose ATG (0.0347 and 0.0517), rituximab (0.0666 and 0.0465), alefacept (0.0817 and 0.112), abatacept (0.0839 and 0.0967), low-dose ATG/G-CSF (0.0889 and 0.0888), low-dose ATG (0.162 and 0.184), and teplizumab (0.166 and 0.144), indicating most potential for low-dose ATG and teplizumab [92]. Finally, only anti-CD3 intervention (teplizumab) has been tested in pre-diabetes stage 2 [49].

Targeting inflammation

The use of various cytokine blockers has been inspired by the positive outcome in other autoimmune conditions such as inflammatory bowel disease and rheumatoid arthritis [93].

Interleukin-1 blockade (anakinra, canakinumab)

Mode of action

Both canakinumab and anakinra induce blockade of IL-1, a key innate immune mediator. Canakinumab is a human monoclonal anti-IL-1 antibody, and anakinra is a human IL-1 receptor antagonist. Because of its direct β-cell pro-apoptotic action and mediatory effects on pancreatic β-cell glucotoxicity, IL-1β has been implicated in the pathogenesis of both type 1 diabetes and type 2 diabetes. No data have been reported so far regarding altered serum levels of IL-1 or other mechanistic outcome measures in studies including individuals with type 1 diabetes.

Pre-diabetes studies

None.

New-onset studies

An exploratory pilot study in 15 children aged 6–18 years tested anakinra 50–100 mg for 28 days in comparison to a historical control group. As a lower insulin dose-adjusted HbA_{1c} was demonstrated after one month's treatment and lower insulin need at

one and four months' treatment [94], the following two randomized placebo-controlled trials in two groups of individuals with recent-onset type 1 diabetes were conducted. Both trials used the baseline-adjusted 2 h AUC C-peptide response to a mixed-meal tolerance test at the end of the study as the primary endpoint.

The individuals in the canakinumab trial were aged 6–45 years and enrolled at 12 sites in the USA and Canada. They were randomized to an SC injection of 2 mg/kg (maximum 300 mg) canakinumab (n = 47) or placebo (n = 22) monthly for 12 months. The difference in 2 h C peptide AUC between the canakinumab and placebo groups at 12 months was 0.01 nmol/l (p = 0.86) [52].

Individuals with type 1 diabetes in the anakinra trial were aged 18–35 years and enrolled at 14 sites across Europe, and randomized to 100 mg anakinra (n = 35) or placebo (n = 34) daily for nine months. The difference in the 2 h C-peptide AUC between the anakinra and the placebo groups at nine months was 0.02 nmol/L (p = 0.71) [52].

No difference was observed in HbA_{1c} comparing the intervention groups to their respective placebo groups.

Safety

In the canakinumab trial the number and severity of adverse events did not differ between groups; however, in the anakinra trial, the individuals receiving anakinra had significantly higher grades of adverse events than the placebo group (p = 0.018), mainly because of a higher number of injection-site reactions.

Tumour necrosis factor α blockade (etanercept, golimumab)

Mode of action

Etanercept is a recombinant soluble TNF-α receptor fusion protein that binds to the TNF-α receptor. It acts by clearing TNF-α from the circulation, thereby blocking the biological activity of this inflammatory cytokine. Golimumab is a monoclonal antibody that binds to both soluble and transmembrane forms of TNF-α and thereby inhibits the effect of TNF-α. No data have been reported regarding altered serum levels of TNF-α or other mechanistic outcome measures in studies including individuals with type 1 diabetes.

Pre-diabetes studies

None.

New-onset studies

A 24-week double-blind, randomized, placebo-controlled pilot study was carried out involving 18 individuals aged 7.8–18.2 years who were randomly assigned to receive either etanercept (0.4 mg/kg max 25 mg SC twice weekly; n = 10) or placebo (n = 8). The percent change in a 2 h C-peptide AUC during a mixed-meal tolerance test from baseline to week 24 showed a 39% increase in the etanercept group and a 20% decrease in the placebo group ($p < 0.05$). HbA_{1c} at week 24 was lower in the etanercept group (5.9% [41 mmol/mol]) compared with the placebo group (7.0% [53 mmol/mol]; $p < 0.05$), with a higher absolute percentage decrease from baseline than in the placebo group (etanercept 0.41% vs placebo 0.18%, $p < 0.01$) [95].

A recent study testing the TNF-α receptor blocker golimumab reached its primary goal [58]. This phase 2, multicentre, placebo-controlled, double-blind, parallel-group trial randomly assigned in a 2:1 ratio children and young adults (age 6–21 years) with newly diagnosed type 1 diabetes to SC golimumab (induction dose 60 mg/m^2 or 100 mg followed by 30 mg/m^2 or 50 mg every second week, depending on weight below or above 45 kg, respectively; n = 56) or placebo (n = 28) for 52 weeks. The 4 h C-peptide AUC (primary goal) differed significantly (golimumab 0.64 nmol/l vs placebo 0.43 nmol/l, $p < 0.001$). A higher percentage of the golimumab group (43%) was in partial remission defined as insulin dose-adjusted HbA_{1c} <9% (75 mmol/mol) than the placebo group (7%, 53 mmol/mol); however, no difference in HbA_{1c} was demonstrated after 52 weeks (HbA_{1c} change from baseline golimumab 0.47% [5 mmol/mol] vs placebo 0.56% [5 mmol/mol]; $p < 0.8$).

Safety

The use of etanercept is considered safe. There were concerns that TNF-α blockade was associated with an increased risk of hypoglycaemic episodes, but this was not confirmed in a large recent study [96]. No severe adverse events were reported in the studies mentioned and frequency of events was similar. Cold symptoms were reported twice as frequently in the etanercept group than the placebo group. Six of nine episodes of abdominal pain were reported by one participant receiving etanercept [95]. This safety profile has been confirmed in trials testing the effect of etanercept in rheumatoid arthritis [97]. Finally, TNF-α blockers are approved for individuals as young as 2 years who have an autoimmune condition [98].

Interleukin-6 blockade (tocilizumab/NCT02293837)

Mode of action

Tocilizumab is a recombinant humanized anti-IL-6 receptor monoclonal antibody [99].

Pre-diabetes studies

None.

New-onset studies

A phase II/III study has been conducted: EXTEND, a randomized trial of IV tocilizumab (8–10 mg/kg) every 4 weeks for 24 months in 136 individuals with newly diagnosed type 1 diabetes (aged 6–45 years). The primary outcome is 2h C-peptide AUC during a mixed-meal tolerance test at 12-month follow-up. This study has been completed, but the results are still awaited.

Safety

Overall the use of tocilizumab has a good safety profile, although an increased risk of infections and a negative influence on the lipid profile have been reported [99].

Interleukin-12/23 blockade (ustekinumab/NCT02117765)

Mode of action

Ustekinumab is a fully human IgG1κ monoclonal antibody blocking the biological activity of IL-12 and IL-23 through their common p40 subunit [100, 101].

Pre-diabetes studies

None.

New-onset studies

Two studies are ongoing. The first is a pilot clinical trial testing different doses of ustekinumab (45 or 90 mg SC) at various time points (0, 4, 16, 28, and 40 weeks or 0, 4, and 16 weeks) in 20 adults with

newly diagnosed type 1 diabetes with a primary outcome of safety. The second study is a phase II/III, randomized trial in 66 adults with newly diagnosed type 1 diabetes (aged 18–25 years) given an IV loading dose of ustekinumab (6 mg/kg) followed by seven SC injections of 90 mg over 48 weeks. The primary outcome is 2 h C-peptide AUC during a mixed-meal tolerance test at 12-month follow-up.

Safety

The safety profile of ustekinumab is considered good, with similar infection rates between placebo and intervention groups and uncommon infusion reactions [100].

Interleukin-21 blockade (+liraglutide) NCT02443155

Mode of action

A human recombinant monoclonal antibody that binds and neutralizes IL-21 [102, 103].

Pre-diabetes studies

None.

New-onset studies

Anti-IL-21 (12 mg/kg IV every 6 wk) and liraglutide (1.8 mg SC daily injection) are being tested in a 2 × 2 factorial design phase II clinical trial involving 308 adults with newly diagnosed type 1 diabetes (aged 18–45 years). The primary outcome is 4 h C-peptide AUC during a mixed-meal tolerance test at week 54 compared to baseline. The trial has been completed, but no study results have been posted.

Safety

In the first-in-human trial, no clear differences in adverse events were observed between participants treated with active drug versus placebo [102].

Antigen-specific therapy

Antigen-specific immunotherapy is not a standard of care in other autoimmune diseases, where a strong need to control disease activity and symptoms has resulted in the pragmatic use of generalized immune modulation. Type 1 diabetes, by contrast, can be managed by exogenous insulin administration. Antigen-specific immunotherapy that suppresses the autoimmune response – that is, by the induction of tolerance – is an attractive approach in type 1 diabetes as it may avoid the off-target effects seen with systemic immunotherapies. Antigen-specific immunotherapies have good safety track records that could support their long-term use.

There is strong evidence for a loss of immunological tolerance at all stages of type 1 diabetes development as the major immunopathological feature of the disease. Several tolerance-inducing strategies for type 1 diabetes have been approached. The antigen can be given orally, intranasally, or by injection (IV, dermal, or SC), although some routes are favoured for being more tolerogenic (e.g. the oral or nasal route).

Antigen delivery in type 1 diabetes may be by whole antigens, peptides, or as carrier complexes, for instance on nanoparticles or as plasmid-encoded DNA vaccine. The precise mode of tolerance induction might be different in each case. Notably, most antigen-based therapies in type 1 diabetes have been administered as native proteins, but emerging data on hybrid peptides and other post-translational and post-transcriptional modifications suggest that modified proteins could be used as tolerogens.

Insulin and glutamic acid decarboxylase 65 (GAD65) have served as the major antigen targets in these approaches. Insulin-based intervention is used as primary and secondary intervention approaches, whereas GAD65 immunization is for secondary and tertiary interventions.

Insulin as a primary antigen was targeted in clinical trials with oral insulin [104], intranasal insulin [41], altered insulin epitopes [105], proinsulin peptides [106], or as IM injection of DNA plasmids encoding proinsulin [107], but has shown limited success. *Post hoc* analysis of trial data has identified subgroups that may benefit from this intervention and more studies are needed to clarify the potential of insulin as a tolerogenic treatment.

Immunization with the islet autoantigen GAD65 conjugated to alum has been tested in several trials [108–110] with different administration routes and in combination with other compounds. GAD-alum has been tested in combination with vitamin D alone [111] or with vitamin D and etanercept [112]. GAD-alum is also being tested in combination with gamma aminobutyric acid (GABA), but overall the different GAD-alum immunization trials have not reached their primary outcome, though findings from subgroup analyses suggest beneficial effects [113].

Antigen-based therapies are appealing for use in combination with other intervention strategies. An example might be synergistic use with a non-specific, immune-modulatory drug designed to act as a tolerogenic adjuvant for the antigen.

Current status of immunomodulatory therapies

The current status of preventive immunomodulatory therapies shortly after the clinical onset of type 1 diabetes (stage 3) is that they demonstrate at best a temporary effect and the long-term outcome is still unsatisfactory. This may be related to various factors, such as the design and timing of the intervention, the target of modulation, and whom to target. Most studies today have focused on individuals with new-onset type 1 diabetes, testing a single drug selected based on a pathogenetic model of the development of type 1 diabetes in a predefined timespan with endogenous secreted C-peptide as the primary endpoint. Increasing data are emerging that this could turn out to be too simplistic an approach. The accumulating evidence that type 1 diabetes is much more heterogeneous than previously assumed should be reflected in future preventive strategies of type 1 diabetes.

Type 1 diabetes as a heterogeneous disease

The heterogeneous nature of type 1 diabetes is a major obstacle to the success of immunotherapies. The progression of type 1 diabetes varies with age, with young children having a more aggressive form. From the DIPP study, nearly all children developing multiple autoantibodies go on to develop type 1 diabetes by 15 years old (>85%) and those developing multiple autoantibodies before the age of 3 years had a further increased rate of disease progression compared with children who developed autoantibodies at older ages [27]. Identification of biomarkers defining rapid and slow progressors within the natural history of type 1 diabetes development is important and will add to the perception of heterogeneity in type 1 diabetes [114]. Similar data have been demonstrated by

the TrialNet Pathway to Prevention Study, where age was identified as the single most important factor for rapid progression in individuals with multiple antibodies, with a significant difference between children and adults [8]. In parallel, the same group observed a similar rate of decline in C-peptide after the clinical onset of type 1 diabetes among individuals aged 7–21 years, whereas participants aged over 21 years had a slower decline in C-peptide [115].

Finally, the significant effect of the intervention with rituximab (anti CD-20) [54] and abatacept (CTLA4-Ig) [60] was mostly driven by the positive response from the paediatric participants. Hence, it is important to note that if the initial intervention studies had been performed exclusively within adults with new-onset type 1 diabetes, a negative result might have been the most likely outcome. The chance of retesting such an intervention within the paediatric population would have been unlikely, thereby discarding a putative positive effect in children. On the other hand, if the trial did not reach the primary goal, typically neither adults nor children achieved any benefit, exemplified by the GAD-alum trial [116]. Furthermore, data related to the insulitis lesion also point towards heterogeneity, as demonstrated among 45 cadaveric type 1 diabetes pancreata with massive variation within the insulitis process [11, 117]. These studies also seem to confirm the apparent discrepancy between β-cell mass and endogenous C-peptide production, as insulin-producing β cells may persist even in individuals who have no detectable levels of C-peptide and with up to 56 years of disease [117]. Within the immune system, there is increasing recognition of distinct endotypes in those with recent-onset type 1 diabetes, reflective of various unique pathobiologies [13, 14]. Finally, even at the β-cell level, several endo-types as a result of various combinations of the autoimmune versus β cell interaction have been hypothesized, spanning from a state of *benign* islet autoimmunity to progression to type 1 diabetes relying on more highly vulnerable β cells [30].

As not all participants in the preventive type 1 diabetes trials have benefited from the tested intervention, new strategies to identify responders versus non-responders are urgently needed and hence the development of better biomarkers is warranted [8]. Also, further characterization of immune phenotypes seems to be of importance in relation to outcome [118].

When to intervene?

It is possible that the modest impact of interventions at clinical onset (stage 3) could be due to the clinical design of mainly testing single drugs in an ineffective dose and not using combination treatment. It is also simply possible that by the time of clinical onset the disease has progressed beyond the point of no return. From the various current trials it has been suggested that individuals with higher baseline C-peptide perform better and the eventual outcome after cessation seems inevitable, suggesting that intervention at an earlier stage as well as possible retreatment might improve the overall outcome [114], the former exemplified by teplizumab intervention in relatives at risk of type 1 diabetes [49].

Future strategies

Preserving β-cell function is an obvious and mandatory endpoint of success in preventing type 1 diabetes from progressing to the clinical phenotype known today. However, it could be speculated that the other side of the coin – that is, insulin sensitivity – plays a role in type 1 diabetes rather than solely the insulin secretion capacity of the remaining β cells. It is thought-provoking that improvement in C-peptide capacity does not always lead to a reduction in HbA_{1c}, indicating, at best, a limited effect of the metabolic outcome exemplified by the teplizumab studies [50, 75]. A more recent observational study evaluated insulin sensitivity before and after treatment with abatacept in individuals with rheumatoid arthritis. Insulin sensitivity, evaluated by the Matsuda Insulin Stimulation Index (ISI), significantly improved after six months of abatacept treatment ($p = 0.003$) [119]. Such observations argue in favour of testing various combinations of interventions aiming at different targets. Testing various combinations of interventions is currently being adopted in long-term follow-ups of NCT02293837 (T1DES): five-year follow-up of AbAte (teplizumab/antiCD3), T1DAL (alefacept/CTLA 4 Ig), and EXTEND (tocilizumab/IL-6 blockade), $n = 80$ in total. These studies are currently recruiting.

Conclusion

Despite tremendous progress in type 1 diabetes disease-modifying approaches, none of the current immunotherapies discussed in this chapter is sufficiently effective alone in preventing or managing type 1 diabetes. An even deeper understanding of the immunopathological processes of type 1 diabetes is needed to tailor innovative and more efficient immunotherapies.

Combination treatment has several potential advantages over monotherapy. It would allow a lower dose of riskier agents as well as rational combinations for complex disease, and has proven efficacy in for instance cancer, HIV, and transplantation. Combination therapy that works through two mechanistic targets seems attractive. One option may be a combination of antigen-specific and systemic immune-modulatory treatment; the latter could target T cells (e.g. anti-CD3) or be anti-inflammatory. Alternatives could be combining immune-modulatory treatment with a β cell–specific treatment or an insulin sensitizer.

It seems reasonable to assume that the lack of success in most of the immunotherapy trials to date relates to the fact that type 1 diabetes is a heterogeneous disease with different disease stages (Figure 76.1). This suggests that a given immunotherapy may not work equally well in all individuals, for example due to genetic or biochemical interindividual variation. Furthermore, a given immunotherapy may not work equally well at different stages of the disease process.

To ensure the efficacy of future trials, an intelligent trial design is critical. Improved biomarkers, including genetic profiling, that reflect disease activity may assist in predicting who is likely to respond to a given immunotherapy (Figure 76.3).

Increased knowledge of the pathogenesis of type 1 diabetes has provided us with better options for more specific prevention of the disease. Currently, therapies targeting effector and regulatory T cells show most promise, but combination therapies, for instance targeting both the immune system and the β cell, may have even larger potential. More extensive biomarker screening to identify likely responders and non-responders to a given therapy will be crucial. Together, this will bring us closer not only to treating type 1 diabetes, but also to preventing and reversing it.

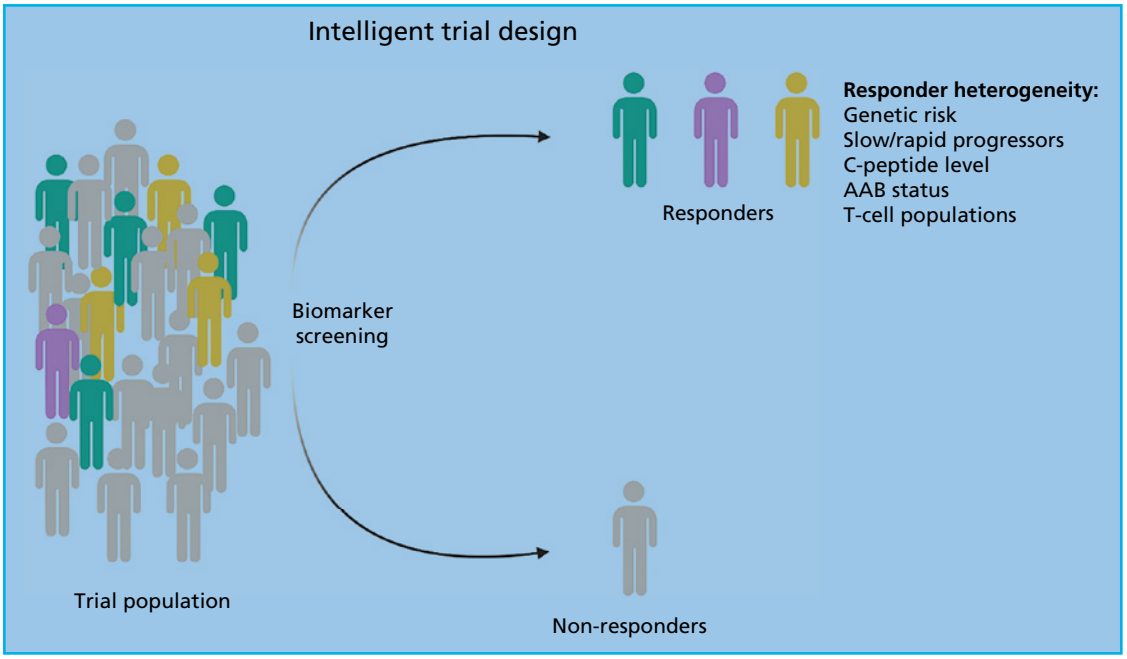

Figure 76.3 The trial population is critical for efficacy of a trial. Improved biomarker signatures will reflect disease activity and will allow for prediction of who will respond to or may have potential severe adverse effects from a particular immunotherapy. AAB, auto-antibody.

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77 Stem Cell Therapy in Diabetes

Angelo Avogaro and Gian Paolo Fadini
Department of Medicine, University of Padova, Padova, Italy

Key points

- Stem cells divide asymmetrically to produce self-renewing cells and daughter cells that differentiate; they can also divide symmetrically to expand the stem cell pool.
- A β cell can be formed by an α cell following the allocation towards the pancreatic lineage.
- A functional β cell can be reprogrammed from adult cell types through an inducible pluripotent state cell.
- Angiogenesis occurs as the sprouting of a small endothelial tube from pre-existing capillary beds in response to local hypoxia, while arteriogenesis is the transformation of pre-existent collateral arterioles into functional collaterals.
- Renal progenitor cells and organoids represent an alternative to modulate kidney regeneration.

Why use stem cells in people with diabetes?

Despite optimal diabetes management, diabetes is associated with the development of chronic complications, reduced quality of life, and an 3.1-fold increased relative risk for mortality for people with type 1 diabetes. The primary unmet clinical needs in diabetes care are:

- To develop a cure for the disease by recreating physiological insulin secretion and normal blood glucose levels to avoid long-term complications.
- To reverse long-term complications in individuals who already have these disabilities.

The treatment for people with type 1 diabetes is daily intensive insulin therapy, with as many as 20% of individuals with type 2 diabetes requiring insulin therapy. The treatment of diabetes with exogenous insulin is often problematic due to unavoidable recurrent hyper- and hypoglycaemic episodes. Therefore, pancreas or isolated islet transplantation is needed to restore normal glucose metabolism in selected individuals with recurrent and often asymptomatic severe hypoglycaemic episodes despite optimal medical therapy and education (Chapter 34). However, pancreas transplantation requires major abdominal surgery and immunosuppression. Islet transplantation is more acceptable because it is less invasive and repeatable, and is indicated for individuals who are ineligible for pancreas transplantation. Unfortunately, these approaches are limited by the number of donor organs and the need for immunosuppression. For these reasons, strategies for β-cell replacement based on stem cells to create insulin-producing cells have been proposed.

What is a stem cell?

Stem cells are undifferentiated cells that give rise to differentiated cells, the *bricks* for building tissue and organs (Figure 77.1). In the postnatal and adult stages of life, tissue-specific stem cells can be found in differentiated organs and are extremely important in tissue repair following injury. Characteristics of stem cells include self-renewal, clonality, and potency (the ability to differentiate into different cell phenotypes) [1]. Stem cells usually reside in a niche environment, which regulates the stem cells by providing short-range signals. In terms of the potential to differentiate, stem cells can be categorized into totipotent, pluripotent, multipotent, oligopotent, and unipotent. Totipotent or omnipotent cells, such as fertilized oocytes, are the most undifferentiated cells in early development. Pluripotent stem cells can differentiate into cells that arise from the three germ layers – ectoderm, endoderm, and mesoderm – from which all tissues develop. Pluripotent stem cells can be generated from reprogrammed somatic cells, called induced pluripotent stem cells (iPSCs). Unlike human embryonic stem cells (hESCs), iPSCs can be generated from tissue biopsies, thus providing a limitless source of person-specific material that can be used to produce specific cell types, such as insulin-producing cells. iPSCs can be generated from different cell types, though many obstacles remain to be resolved before taking full advantage of this technology in therapy [2].

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Multipotent cells, such as mesenchymal stem cells (MSCs), are ubiquitous and can differentiate into cells from a single germ layer. Oligopotent stem cells can self-renew and form two or more lineages within a specific tissue; haematopoietic stem cells are oligopotent stem cells, as they can differentiate into myeloid and lymphoid lineages. Unipotent stem cells can self-renew and differentiate into only one specific cell type and form a single lineage, such as endothelial progenitor cells (EPCs) [3].

Stem cells for insulin replacement

Many protocols for efficient differentiation of stem cells into functional endocrine cells have been developed [4], but most have not generated fully functional β cells [5]. The differentiation of human pluripotent stem cells to pancreatic cells is obtained through a series of steps mimicking *in vivo* development (Figure 77.2).

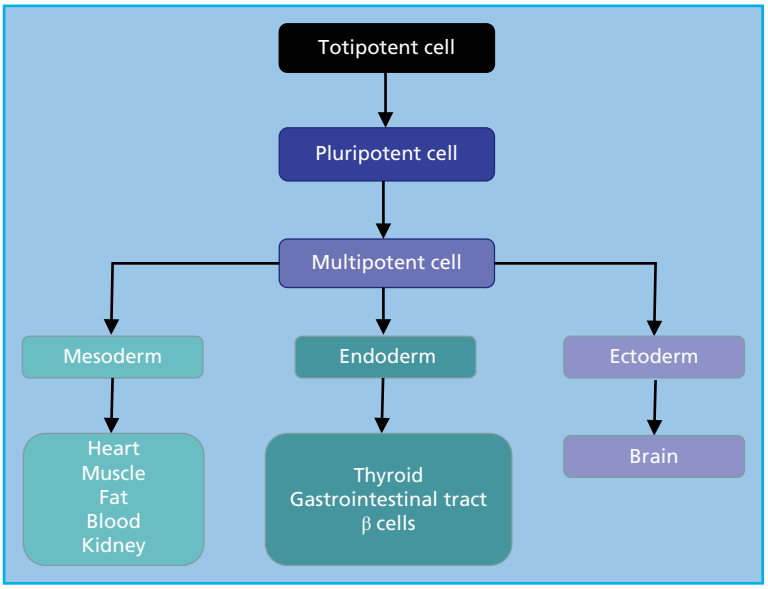

Figure 77.1 Pluripotent stem cells can differentiate into cells that arise from the three germ layers – ectoderm, endoderm, and mesoderm – from which all tissues develop. Pluripotent stem cells can be generated from reprogrammed somatic cells, called induced pluripotent stem cells.

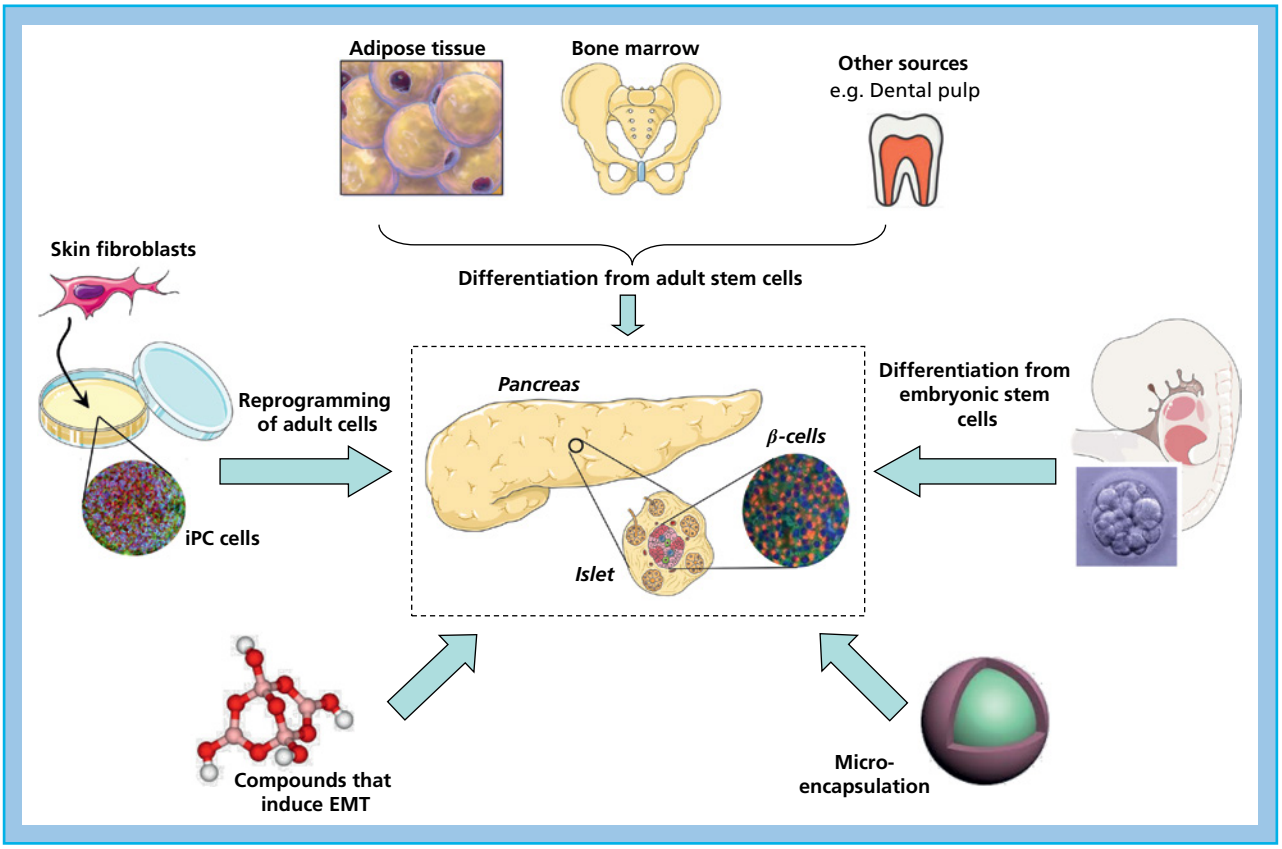

Figure 77.2 Cell phenotypes and organ able to generate functional β cells. EMT, epithelial-to-mesenchymal transition; iPC, induced pluripotent cell.

These steps lead to the formation of definitive endoderm, characterized by:

- Expression of the transcription factors forkhead box A2 (FOXA2) and SRY-box transcription factor 17 (SOX17) and the cell surface marker C-X-C motif chemokine receptor 4 (CXCR4).
- Patterning of the posterior foregut to generate pancreatic and duodenal homeobox 1 (PDX1)-expressing endoderm.
- Specification of the PDX1+ endoderm to pancreatic progenitors expressing PDX1 and NK6 homeobox 1.

Endocrine commitment is characterized by the upregulation of neurogenin-3 and NK2 homeobox 2, followed by the expression of lineage-specific genes, including the hormones insulin expressed by β-like cells, glucagon expressed by α-like cells, and somatostatin expressed by δ-like cells [6]. Each step is controlled by the activation and/or inhibition of specific pathways. Activin/nodal and canonical Wnt signalling are required to form definite endoderm, whereas retinoic acid and fibroblast growth factor 10 signalling are essential for PDX1 induction (Figure 77.3). Endocrine lineage commitment is achieved in the presence of bone morphogenetic protein (BMP)/transforming growth factor β (TGF-β)/Notch inhibition. Cultures obtained with these sequential procedures are composed of β-like cells and other cell phenotypes such as endocrine cells, uncommitted progenitors, and enterochromaffin cells.

Cells generated with these protocols secrete human C-peptide in response to glucose, and can rescue hyperglycaemia in streptozotocin-diabetic mice [7]. MSCs have also been used to generate insulin-producing cells [8], as well as to enhance islet engraftment and survival, and to improve metabolic control in experimental diabetes [9]. Trials performed in type 2 diabetes suggest a positive impact of bone marrow–derived mononuclear cells on metabolic measures in the absence of adverse events, following intra-arterial injection by selective cannulation of the pancreatic vasculature [10]. Rezania et al. have demonstrated that pancreatic progenitor cells can produce glucose-responsive, insulin-secreting cells and prevent or reverse diabetes in mice [11]. An alternative strategy is the reprogramming of terminally differentiated cell types into β cells. Zhou and Melton showed a direct conversion of mouse acinar cells to β cells *in vivo* via viral expression of particular genes; these induced cells were able to improve glycaemic levels in diabetic mice [12]. A further example of adult cell reprogramming to β cells has been described for adult mouse α cells. Following the allocation to the pancreatic lineage, the endocrine differentiation program is initiated through the expression of neurogenin-3 (*NGN3*), and $NGN3^+$ cells can become α cells or bipotential β/δ precursors [13]. Combining several lineage-tracing approaches, authors have shown that pancreatic duct-lining precursor cells are continuously mobilized, re-express the developmental gene *NGN3*, and successively adopt a glucagon-expressing and β-like cell identity through mechanisms involving the reawakening of the epithelial-to-mesenchymal transition [14]. The restoration of insulin-producing cells from non-β-cell origins is enabled throughout life via δ- or α-cell spontaneous reprogramming, suggesting a condition with multiple intra-islet cell interconversion events. A further approach to make functional β cells is to reprogram adult cell types towards β cells; any tissue could be reprogrammed to iPSCs. Differentiation protocols can be applied to human iPSCs: cell lines derived from reprogrammed human fibroblasts have been successfully differentiated to insulin-producing cells *in vitro* [15, 16].

Maehr et al. have shown that fibroblasts obtained from skin biopsies from two individuals with type 1 diabetes were reprogrammed to pluripotency and differentiated to insulin-producing cells, although their functionality needs further validation [17]. In this context, Hua et al. generated iPSCs from people with maturity-onset diabetes of the young type 2 (MODY-2); these stem cells differentiated into β cells with an efficiency comparable to that of controls and expressed markers of mature β cells.

β-cell replacement therapy can be considered a viable treatment option for individuals with β-cell failure and severe and persistent glycaemic instability despite optimal high-quality medical care and education. After the transplant, β-cell survival is crucial and still represents a significant barrier to cell replacement therapy. There is a 60% loss within the first few days after transplant, probably determined by hypoxia following alteration in the vascularization of transplanted cells. Another challenge is the allo-rejection and autoimmune reaction, which can be present when hiPSC-derived cells are transplanted into individuals with type 1 diabetes. Encapsulation could potentially overcome this challenge, since it would provide a physical barrier between the host and the transplanted β cells [18]; these devices should contain pore sizes that permit the exchange of oxygen, glucose, and insulin, but at the same time would not allow the transit of immune-competent cells and molecules responsible for mediating the immune rejection. The potential drawback is the presence of hypoxia in the centre of the device and the host-mediated fibrosis around the capsule. ViaCyte's Encaptra device comprises a single immuno-isolating membrane that protects cells from direct physical contact with host immune cells; this device is currently in clinical trials with hPSC-derived progenitor cells (ClinicalTrials.gov identifier NCT02239354).

While macrocapsules have shown adequate vascularization, limited fibrosis, and immunoprotection, microcapsules, made by

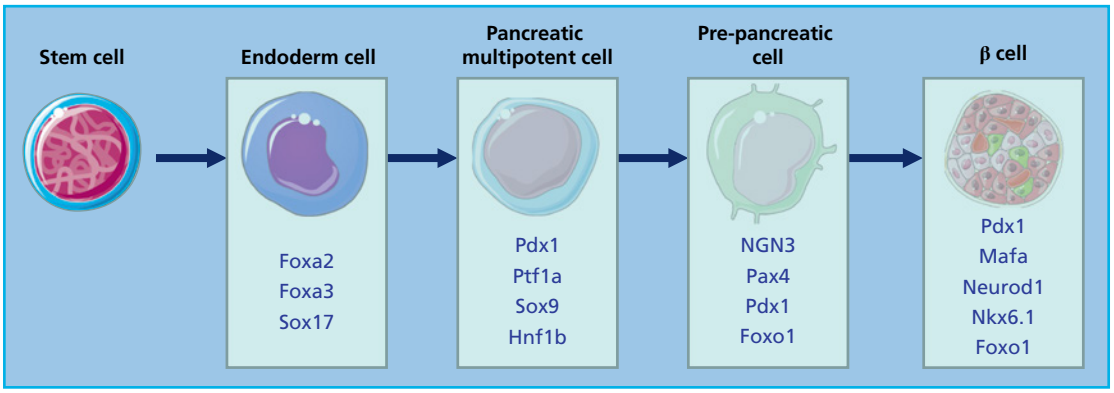

Figure 77.3 Transcription factors responsible for transition from stem cells to fully functional β cells.

alginate, a natural polysaccharide with good biocompatibility, contain 1–3 islets, are approximately 300–1500 mm in diameter, should confer improved diffusion characteristics compared to extravascular macrocapsules, and involve minimally invasive procedures to be implanted [19]. Since microcapsules are tiny, one potential problem is their retrievability after implantation, raising safety concerns. Semma Therapeutics/Vertex received approval to launch a clinical trial to test its human pluripotent stem cell–derived β-cell product's (VX-880) safety, tolerability, and efficacy when infused into the hepatic portal vein of individuals with type 1 diabetes (ClinicalTrials.gov identifier NCT04786262).

For islet transplantation, 5000 islet equivalents (IEQs)/kg of the recipient body mass should be transplanted for adequate glycaemia, with yields of >7000 IEQ/kg from a single donor correlating with a higher likelihood of resulting in insulin independence [20]. For an adult weighing 75 kg, this would represent a fraction of the total mass of an endogenous β cell, meaning that only a small cell population may guarantee insulin independence. Multiple transplantation sites are being pursued as options for stem cell–derived insulin-producing cells. Microcapsules are often transplanted into the peritoneal cavity. Intravascular macrocapsules are connected as a shunt to the systemic blood circulation, whereas extravascular microcapsules are typically implanted subcutaneously or intraperitoneally.

Subcutaneous, intramuscular, and omental/intraperitoneal sites are similar candidates for hPSC-derived insulin-producing cells. Subcutaneous implantation offers the advantages of retrievability and simplicity of delivery, but the major challenge can be poor spontaneous vascularization. A significant aim is the tolerance of transplanted human pluripotent stem cell–derived β-like cells. Genetic approaches are being developed to enable human pluripotent stem cell–derived and differentiated progeny to escape detection from alloimmune effectors following transplantation. Gene editing techniques have been proposed to decrease the expression of human leucocyte antigen (HLA) proteins on the surface of human pluripotent stem cell–derived cells and their progeny. The same approach can be used to control the expression of various immunomodulatory factors by the implanted human pluripotent stem cell–derived cells. Other strategies include cellular immunotherapy by using monoclonal antibodies targeting T-cell co-stimulatory pathways.

Two companies have initiated clinical trials with stem β cells. A European consortium started a trial where pancreatic progenitor cells (PEC 01) cells are encapsulated into an open device, allowing the growth of new blood vessels while administering both anti-inflammatory agents and standard immunosuppression [21]. The β-Cell Therapy Consortium announced that VC-02™ had been implanted into people with type 1 diabetes for the first time in Europe, meaning that human-induced pluripotent stem cell–derived insulin-producing cells can survive, engraft, differentiate, and mature into human islet-like cells when implanted subcutaneously. Vertex also announced that a new approach based on fully differentiated and functional stem cell–derived islet-like organoids (VX-880) delivered through the portal vein combined with immunosuppression would be tested in humans [22].

Healing the heart

Diabetes doubles the risk of cardiovascular disease, regardless of other risk factors, with the risk being more significant in women, those of a younger age, and those with long-lasting diabetes and microvascular complications. As a consequence of coronary heart disease, heart failure is also more prevalent in people with diabetes. For these reasons, cardiac regenerative medicine is of primary importance in diabetes. During an acute myocardial infarction, billions of cardiomyocytes are lost, and current therapies cannot re-establish such a loss. Ageing also causes cardiomyocyte loss. Myocyte apoptosis in the normal human heart involves at least 1 in 100 000 cells at any time, which equals a decrease of 2.2% of myocytes per year [23]. Ischaemia is determined by significant obstruction of the coronary blood flow during myocardial infarction with an irreversible loss of cardiomyocytes. Because the heart is a terminally differentiated organ with little to no regenerative capacity, the remaining cardiomyocytes cannot replace the lost cells. Therefore, compensatory scarring replaces the dead tissue, leading to compromised cardiac function and heart failure.

The approach to cardiac regenerative medicine with stem cells has been disappointing to date. However, in light of the rising incidence of heart failure and a simultaneous shortage of organs, the option of a regenerative approach remains more relevant than ever [24]. Stem cells, defined by their ability to self-renew and differentiate into at least one other cell type, were investigated for their ability to replace lost myocardium directly. In pre-clinical models, stem cell therapy improves left ventricular ejection fraction by 7.5% in large animal models and from 2% to 5% in clinical trials. The stem cells used for cardiac regenerative purposes are divided into first, second, and subsequent stem cells. First-generation stem cell therapy was based on skeletal myoblasts, bone marrow mononuclear cells, adipose tissue–derived regenerative cells, mesenchymal stem cells, and haematopoietic stem cells ($CD134^+/CD133^+$). Second-generation stem cells include purified cardiac cell populations such as $ckit^+$ cardiac stem cells, cardiosphere-derived cells, pluripotent cells, and allogeneic cells. Next-generation stem cells have modified and lineage-directed stem cells, such as cardiopoietic stem cells derived from mesenchymal stem cells; this generation also includes combination therapy of specific cell types. Several trials have been completed, but the results were, at best, unequivocal in terms of left ventricular ejection fraction, scar size, or left ventricular volume improvement [25].

As an alternative to cell therapy, the use of drugs is being considered to modulate stem/progenitor cell availability and homing. Zaruba et al. proposed a combined strategy of granulocyte colony-stimulating factor (G-CSF) plus dipeptidyl peptidase 4 (DPP-4) inhibition to improve cardiac homing of mobilized stem/progenitor cells, which is currently under clinical investigation in the SITAgliptin plus GRanulocyte colony-stimulating factor in patients suffering from Acute Myocardial Infarction (SITAGRAMI) trial in individuals after acute myocardial infarction [26]. This approach stems from the concept that inhibition of DPP-4, which cleaves the primary stem cell attracting chemokines, stromal-derived factor-1 α (SDF-1α), will improve the homing of mobilized stem/progenitor cells. Endogenous stem cell mobilization can also be achieved using the CXCR4 antagonist plerixafor. The cardiac stem/progenitor cells (CSPC) compartment is involved in diabetic cardiac dysfunction by activating the cell death pathways and inhibiting cell replication [27]. Glucose-induced dysfunction of the pool of CSPCs leads to insufficient replacement of old, dying cells and acquisition of the heart senescent phenotype. A protein that appears to be implicated in CSPC poll damage is p66shc, an adaptor protein, which is linked to premature ageing, oxidative stress, and apoptosis. Exposure of human CSPCs to hydrogen peroxide results in increased caspase-3 cleavage and apoptosis, mediated by the activation of the c-jun

N-terminal protein kinase (JNK) pathway [28]. Regarding cell bioenergetics, CSPCs exposed to a diabetic environment show remarkably reduced activity of key enzymes of the pentose phosphate pathway (G6PD and transketolase), resulting in decreased antioxidant defence mechanisms and activation of apoptosis [29]. Inflammation is also being implicated [30].

Creating new vessels

Peripheral arterial disease is highly prevalent among people with diabetes and is associated with significant morbidity and mortality. Peripheral arterial disease can lead to critical limb ischaemia, resulting in substantial amputations and death. Angiogenesis and arteriogenesis should represent compensatory mechanisms to increase vessel growth in individuals with peripheral arterial disease. Angiogenesis occurs as the sprouting of the small endothelial tube from pre-existing capillary beds in response to local hypoxia. It is mainly mediated by vascular epithelial growth factor (VEGF), with no need for non-tissue-resident cells. The resulting capillaries are tiny, and cannot compensate for any sizeable occluded conduit artery. Arteriogenesis is the transformation of pre-existent collateral arterioles into functional collateral arteries. This implies an increase in the diameter of existing arterial vessels capable of compensating for the loss of function of occluded arteries. Ischaemia itself induces elevated plasma stem and progenitor cell-activating cytokines, including sKitL (soluble Kit ligand) thrombopoietin, and G-CSF. Together with hypoxia, these in turn generate the release of SDF-1, thereby stimulating the mobilization of proangiogenic cells that accelerate revascularization of the ischaemic site [31].

One approach to stimulate angiogenesis is to administer locally proangiogenic factors such as growth factors and cytokines, including vascular endothelial growth factor, fibroblast growth factor 2, and TGF-β. Unfortunately, this approach has essential drawbacks, such as dosing problems, poor local retention, and high cost. Another method is based on the administration of genes rather than proteins by using plasmid-based or viral carriers, but, similarly, dosing problems and tissue retention remain significant issues. An additional approach is the administration of bone marrow–derived and adipose-derived stem cells. Traditional circulating EPCs originated from the monocyte–macrophage lineage [32]. Circulating stem cells (CSCs) are a heterogeneous cellular population within peripheral blood with different anatomical and developmental origins. Haematopoietic stem and progenitor cells (HSCs/HSPCs) constitute the most abundant and best-characterized CSC type [33]. HSCs/HSPCs retain migratory activity during adulthood. They circulate in the blood and can be found in various organs such intestine, liver, lungs, kidneys, and skin. HSPCs contribute to peripheral tissue homeostasis by regulating vascular repair and regeneration [34]. This hypothesis, which is relevant to the relationship between CSCs and cardiovascular outcomes, is supported by the aforementioned ontological overlap between the haematopoietic and vascular systems. Over the last two decades, CSCs have been extensively studied in three main areas of cardiovascular research:

- Physiological contribution to myocardial and vascular homeostasis.
- Experimental and human cell therapies for the treatment of cardiac or peripheral ischaemia.
- Clinical biomarkers for diagnosis and prognosis.

Beyond their ability to physically repair the damaged blood vessels, CSCs exert much of their activity via paracrine signals; most proangiogenic effects of CSCs in peripheral ischaemia appear to be mediated by secretory activity. Pre-clinical findings with bone marrow–derived CSCs, mainly HSPCs and EPCs, have propagated several clinical trials of bone marrow–derived cell therapy for cardiac or peripheral arterial disease. Overall, positive results of cell therapy in chronic ischaemic heart and peripheral arterial diseases support the scientific claim that CSCs are involved in cardiovascular homeostasis [35]. Exposure to virtually any known modifiable cardiovascular risk factors impacts CSC- or EPC-like phenotypes: accelerated CSC senescence and impaired endothelial repair capacity have been demonstrated among people with essential hypertension, cigarette smoking, hypercholesterolaemia, and diabetes. Indeed, diabetes is one of the traditional risk factors most strongly associated with quantitative defects and functional impairment of CSCs, including EPCs. Several studies have consistently reported a reduction of $CD34^+$ CSCs and other progenitor cell phenotypes in the peripheral blood of individuals with type 1 diabetes or type 2 diabetes compared with those without diabetes. This alteration occurs early in the natural history of type 2 diabetes, is only partially reversible with glucose management, and becomes more profound in long-standing complicated diabetes. Reversal of these risk factors may overcome the intrinsic deficiencies of autologous EPCs. Attention should be paid to the application of EPCs in advanced cardiovascular states, with a special effort to optimize cell therapy's metabolic and mechanical context. Standard treatment for severe cases of peripheral arterial disease is surgical or endovascular revascularization. Nonetheless, up to 30% of individuals are not candidates for such interventions due to high operative risk or adverse vascular anatomy. Bone marrow–derived stem and progenitor cells have been identified as potential therapeutic options to induce angiogenesis.

In humans, two different approaches have been proposed, based on (i) unselected autologous mononuclear bone marrow–derived stem cells (BM-MNCs) directly sampled from bone marrow; or (ii) autologous $CD34^+$ or $CD133^+$ BM-MNCs sampled from peripheral circulation after G-CSF stimulation of the bone marrow. Cells can be administered intra-muscularly, intra-arterially, or topically (Figure 77.4). The intramuscular approach is easily performed and allows a significant amount of cells to be injected in the proximity of the ischaemic area; theoretically, this approach may result in a cell depot, which would allow local paracrine activity.

The first clinical trial of stem cell therapy in peripheral arterial disease was the Therapeutic Angiogenesis using Cell Transplantation (TACT) study, with unselected BM-MNCs injected intramuscularly into the ischaemic limbs of individuals with critical limb ischaemia; it proved safe and improved rest pain, perfusion, oxygen pressure, and pain-free walking distance at 24-week follow-up compared with placebo [36]. One clinical trial using unselected BM-MNCs delivered intra-arterially demonstrated a similar improvement in ankle-brachial index (ABI) compared with previous trials of intramuscular BM-MNC administration [37]. Notably, an intra-arterial study in people with diabetes suggested much more significant ABI improvements, as well as an improvement in wound healing and blood flow. The Intraarterial Progenitor Cell Transplantation of Bone Marrow Mononuclear Cells for Induction of Neovascularization in Persons With Peripheral Arterial Occlusive Disease study has been a multicentre, randomized trial of intra-arterial BM-MNC therapy in people with critical limb ischaemia [38]. The study reported improvements in wound healing and

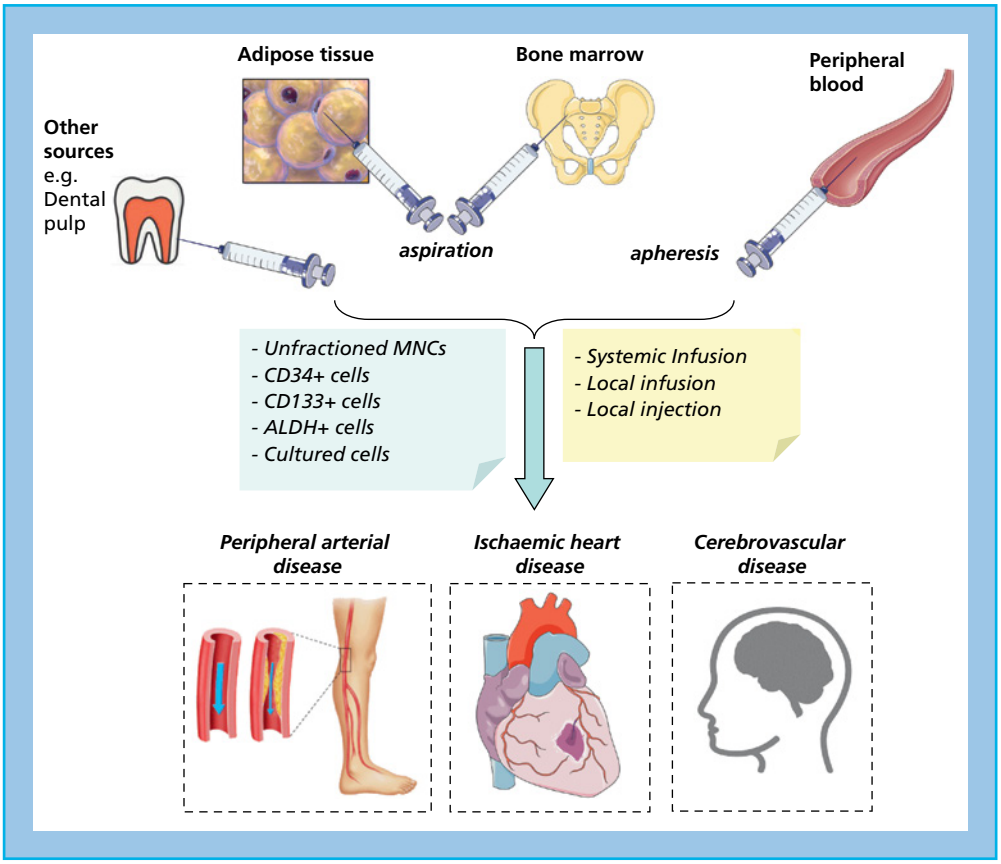

Figure 77.4 Stem cell–based and growth- and chemokine-based therapeutic approaches to regenerate the cardiovascular system. ALDH, aldehyde dehydrogenase; MNC, mononuclear cell.

reductions in rest pain, despite no effect on ABI and limb salvage rates. Both intramuscular injection and intraarterial injection of G-CSF mobilized peripheral MNCs, resulting in a >0.1-point improvement in ABI and a twofold increase in maximum walking distance in small clinical series.

A meta-analysis by Fadini et al. from 37 cell therapy trials indicates that cell therapy can significantly improve ABI, transcutaneous oxygen, rest pain, pain-free walking distance, ulcer healing, and limb salvage [35]. In contrast, G-CSF monotherapy was not associated with significant improvement of these endpoints, albeit conclusions should be deferred because the number of G-CSF testing trials was limited. High aldehyde dehydrogenase (ALDH) activity identifies a subset of blood-derived progenitor cells with high vascular regenerative potential; ALDH is an intracellular detoxification enzyme highly expressed by progenitor cells from multiple mesodermal lineages that protects differentiating progenitor cells from damage by alkylating agents or oxidative stress [39]. A clinical trial performed for severe critical limb ischaemia demonstrated that intramuscular implantation of autologous bone marrow ALDH cells improved Rutherford category scores and ABI at 12 weeks post-transplantation [40].

Lately, attention has been devoted to the role of extracellular vesicles produced by human EPCs and MSCs; these extracellular vesicles contain potent regenerative cargo in the form of proteins, lipids, and microRNAs. They are released by membrane blebbing or exocytotic mechanisms and may have a potential role for vascular repair since they release $CD34^+$ cells. Mathiyalagan and colleagues injected mice with purified $CD34^+$ cell exosomes and showed improved hindlimb perfusion and preserved muscle mass [41]; they demonstrated that $CD34^+$ cell-derived exosomes contained high levels of miR-10a and miR-130, with previously demonstrated antifibrotic activities in the ischaemic myocardium. Future studies will reveal the potential of extracellular vesicles in vascular repair and regeneration.

Stem cell–based therapy for kidney disease

An estimated 840 million people worldwide have chronic kidney disease, which was responsible for 1.2 million deaths and 35.8 million disability-adjusted life years in 2017. Diabetes is a significant risk factor for chronic kidney disease, and ~20–40% of people with diabetes have evidence of chronic kidney disease. Chronic kidney disease does not remit spontaneously and gradually progresses to end-stage renal disease (ESRD) without intervention. The adult human kidney has a limited number of nephrons, determined during embryonic development by many genetic and environmental factors that cannot be modified after the 36th week of gestation. This inherent incapability of total kidney regeneration pushes towards the application of strategies for kidney regeneration. ESCs represent a strategy for kidney regenerative therapies. They are capable of differentiation into different kidney mature cell types. Most protocols of human ESC differentiation to kidney cells have been translated from studies in mice; however, significant concerns such as ethical issues have significantly limited their use. They also are at high risk of degenerating in neoplasms, especially teratomas, and eventually, since differentiated cells are allogeneic, they suffer from all the issues related to allografts and immunocompatibility.

iPSCs can generate cells that resemble renal progenitors and their progenitors, such as podocytes and tubular epithelial cells [42]. Although iPSCs have the advantage of having the same genetic background as the individual they are derived from, a major concern is the presence of an epigenetic memory, such as methylation/demethylation, which may affect the ability of iPSC-derived mature cells to reliably recapitulate the disease pathophysiology, but also the differentiation capability. One possibility is the generation of kidney-derived iPSCs that would retain the specific renal epigenetic memory of the cell of origin.

Kidney organoids are essential tools for studying the development of the human kidney [43]. Organoids are self-organizing 3D aggregations of cells representing the structure and function of organs. They can be derived from ESCs or induced by iPSCs. Many protocols have been proposed for the induction of kidney organoids from iPSCs; the availability of technologies such as single-cell RNA sequencing has provided insights into the relevance of kidney organoids to the process of kidney development. Kidney organoids can advance the field of nephrology for regenerative therapy. Nevertheless, significant barriers remain to using organoids for any of these purposes.

Kidney organoids have been successfully used to model glomerular and tubular diseases. Advances in single-cell RNA sequencing have led to identifying various cell types in the organoids. They have been shown to be similar to, but more immature than, human kidney cells *in vivo*. Now protocols are available that enable the successful generation of ureteric bud from mouse ESCs and human iPSCs. Combining nephron progenitor cells and ureteric bud generated from mouse ESCs with mouse embryo-derived stromal cells makes it possible to create kidney organoids that show both ureteric bud branching and differentiated nephrons [44]. Although promising, significant obstacles remain: scRNA-seq and transcriptional profiling studies have demonstrated that organoids represent a very immature kidney system. Therefore, kidney organoids do not generate the full complement of renal cells. A better understanding of organ development and the molecular mechanisms of maturation will be able to be used to develop more mature organs containing a complete complement of renal cell types.

Conclusion

Significant advances have been made recently in stem cell biology and its therapeutic application in the treatment of diabetes and its complications. A tremendous amount of work is still ahead to apply stem cell therapy to people with diabetes on a widespread basis. Common therapeutic strategies for the replacement of β cells and for the rescue of blood vessels and myocardium require totally safe cellular approaches. This is particularly relevant to the deployment of the iPSC approach. However, great uncertainties remain over which precise lineage to employ and the proper conditions that need to be created to yield the optimal therapeutic approach. This is important to new vessel formation since, as described in detail by Fadini et al., the endothelial progenitor is a dynamic phenotype in space and time [45]. Furthermore, other phenomena such as endothelial-to-haematopoietic or epithelial-to-mesenchymal transitions should also be considered, which needless to say underlie the incredible challenges we have ahead before definitively implementing cellular treatment for people with diabetes. Even so, the gap is progressively closing.

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78 Gene Therapy for Diabetes

Veronica Jimenez[1,2] and Fatima Bosch[1,2]

[1] Center of Animal Biotechnology and Gene Therapy and Department of Biochemistry and Molecular Biology, Universitat Autònoma de Barcelona, Bellaterra, Spain

[2] Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Madrid, Spain

Key points

- The term gene therapy defines any therapeutic strategy based on the genetic modification of a cell by introduction of exogenous genetic material to prevent, correct, or ameliorate the symptoms of a disease.
- The selection of one gene transfer vector over another depends on the indication, the target tissue in the case of *in vivo* gene therapy, and the period of time during which the expression of the transferred genetic material is required.
- The use of gene transfer technologies has allowed the development of potential therapeutic strategies for the treatment of type 1 diabetes and type 2 diabetes, as well as the performance of proof-of-concept studies in small and large animal models to understand the pathophysiology of these diseases better.
- For type 1 diabetes, most gene therapy strategies have focused on restoring insulin production by islets or surrogate cells, enhancing glucose disposal, or preventing the destruction of the remaining β cells.
- For type 2 diabetes, gene therapy approaches have been directed towards ameliorating insulin resistance and glucose tolerance, enhancing energy expenditure, and improving adipose tissue dysfunction and inflammation.
- Extensive studies are required to demonstrate the efficacy and safety in large animal models of the approaches that have shown therapeutic potential in small diabetic animals before any of these gene therapies are brought to the clinic to treat diabetes in humans.

Gene therapy is a therapeutic strategy based on the genetic modification of a cell by introduction of exogenous genetic material to prevent, correct, or ameliorate the symptoms of a disease. Originally, gene therapy was conceived to supplement or replace the function of a defective gene by delivering to the target cell a functional copy that could mediate the production of the desired therapeutic protein. Progress in the field has led to a broadening of gene therapy applications, and nowadays the introduction of genetic material to a cell is not only limited to gene addition, but also includes induction, repression, and modulation of gene expression at transcriptional and post-transcriptional levels and, more recently, genome editing. To these ends, full-length genes, cDNAs, mRNA, a variety of modulatory and interfering RNA and DNA molecules – including antisense RNA, short-hairpin RNA (shRNA), microRNA (miRNA), and microRNA target sequences (miRT) – and genome editing endonucleases – zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and the clustered regularly interspaced short palindromic repeats-associated Cas protein system (CRISPR/Cas) – have been used. Furthermore, the vast range of technologies that the field has developed over recent years for therapeutic purposes are also being exploited in proof-of-concept studies to demonstrate gene function.

On the basis of the strategy used, gene therapy can be classified into the following two subtypes: *ex vivo* gene therapy, in which target cells are genetically modified *in vitro* before transplantation into the patient; and *in vivo* gene transfer, in which cells are genetically modified *in situ* in the individual [1].

The success of gene therapy depends on the existence of gene transfer vehicles capable of safely and efficiently introducing genetic material into target cells either *ex vivo* or *in vivo*. To achieve this goal, a wide variety of vectors have been developed over the past few years; these are divided in two main categories: non-viral and viral vectors. Delivery systems based on non-viral vectors include both the direct administration of naked nucleic acids and the use of physico-chemical means to ferry the genetic material into the target cell, such as electrotransfer or incorporation of nucleic acids into liposomes or cationic polymers. The use of viral vectors exploits the natural ability of viruses to enter cells, transfer their genetic material to the nucleus, and express proteins. So far the vast majority of gene therapy strategies developed for the treatment of diabetes have been based on the use of viral vectors as gene transfer vehicles.

Viral vectors

Several naturally occurring viruses have been subjected to numerous genetic modifications to allow their use as safe gene transfer vehicles. Viral vectors cannot develop a pathogenic infection after

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delivery to cells or animals due to the genetic deletion of genes essential for the life cycle of the wild-type virus. Therefore, recombinant viral particles contain a genetically modified viral genome that may be partially or completely devoid of viral genes and is unable to generate new virions on infection. They retain, however, the infectivity of the wild-type virus and its ability to mediate introduction of the genetic material into the cell nucleus (a process known as transduction), because these functions are conferred by the capsid itself [2].

The selection of one vector over another depends on the gene transfer application, the target tissue in the case of *in vivo* gene therapy, and the period of time during which the expression of the transferred genetic material is required. For example, for proof-of-concept studies or if short-term expression is sufficient, adenoviral vectors (AdV) show great efficiency of transduction *in vitro* and *in vivo*. However, the immunogenicity of these vectors precludes their use for therapeutic purposes [3], particularly in the context of chronic diseases such as diabetes.

For therapeutic, *in vivo* approaches in which long-term gene expression is desired, adeno-associated vectors (AAV) stand out as the vectors of choice. The wild-type virus is non-pathogenic and the different serotypes of vectors have the ability to transduce a wide variety of cell types, mediating long-term expression of the gene of interest in non-dividing tissues. In addition, the simple composition of AAV vectors, and their low efficiency in transducing antigen-presenting cells (APCs), may contribute to their generally low immunogenicity [4]. These gene transfer vectors have been used in clinical trials since the mid-1990s, and no serious adverse events related to the vectors have been described so far. More than 3000 individuals have been enrolled in these studies, comprising adults and children affected by different pathologies, generally all serious illnesses, and administered with recombinant AAV at different doses and through different routes to target different organs, mainly liver, skeletal muscle, brain, and eye [5–7]. Thus, recombinant AAV vectors are regarded as having a strong safety record after both local and systemic administration [5–7]. Indeed, three out of the seven gene therapy treatments approved for commercialization are AAV-based therapies [6]. In 2012 the European Medicines Agency (EMA) gave marketing approval to alipogene tiparvovec, the first gene therapy product for the management of lipoprotein lipase deficiency based on the administration of lipoprotein lipase-expressing AAV vectors of serotype 1 (AAV1) to the muscle [6]. In 2017, the AAV2-based voretigene neparvovec-rzyl became the first Food and Drug Administration (FDA)-approved gene therapy for RPE65-mediated inherited retinal dystrophy; in 2018, this product also received market authorization from the EMA [8]. In 2019, the AAV9-based onasemnogene abeparvovec to treat spinal muscular atrophy in children was also authorized by the FDA [6]. Moreover, dozens of other AAV-based treatments are under clinical trial [6, 7].

The only limitations to the use of these vectors are their limited cloning capacity, the presence in the general population of pre-existing anti-AAV humoral immunity due to natural infection that may preclude transduction of certain organs, and the subclinical activation of capsid-specific T cells when vectors are administered to peripheral organs that can limit expression of the therapeutic transgene, although this has so far been efficiently controlled with short-course immunosuppression [9–11].

The main properties of the viral vectors most commonly used in gene therapy are summarized in Table 78.1.

Gene therapy for diabetes

Both type 1 diabetes and type 2 diabetes are characterized by hyperglycaemia, which, when not properly managed, may ultimately lead to the development of long-term complications with high morbidity and mortality. Although the management of hyperglycaemia remains the main target of strategies developed so far for diabetes, several approaches target other components of the disease pathogenesis, which are different in type 1 diabetes and type 2 diabetes, as discussed later.

Gene therapy for type 1 diabetes

The hyperglycaemia of type 1 diabetes results from an absolute deficiency of insulin secretion due to the autoimmune destruction of the β cells of the pancreas. Therefore, the main gene therapy approaches developed for type 1 diabetes have focused on restoring insulin production by islets or surrogate cells, enhancing glucose disposal, or avoiding the destruction of the remaining β cells.

Ex Vivo genetic engineering of islets for transplantation

Islet transplantation has demonstrable therapeutic benefit in people with type 1 diabetes, particularly with the Edmonton Protocol [12]. However, the scarcity of cadaveric donors and the large quantities of functional islets required for amelioration of diabetes in each single individual have limited the broad clinical application of this approach. Moreover, the processes of islet isolation, purification, and transplantation, together with the host's immune response, greatly impair islet function and promote islet apoptosis, limiting the long-term survival of the grafts [12]. To overcome these limitations, several studies have explored gene therapy strategies based on the *ex vivo* genetic engineering of islets prior to transplantation. Adenoviral vectors have been the most extensively used vectors to this end because of their high efficiency for *ex vivo* transduction of islets of different species, including humans [13–15]. Recently, the generation of a chimeric AAV vector displaying markedly enhanced human islet transduction efficiency has been reported [16]. The transgenes used to improve the outcome after transplantation can fall into three main categories:

1. Mitogenic and/or pro-survival/anti-apoptotic factors aimed at promoting islet survival, such as hepatocyte growth factor (HGF), X-linked inhibitor of apoptosis (XIAP), manganese superoxide dismutase (MnSOD), B-cell lymphoma 2 (Bcl-2), and haem oxygenase-1 (HO-1) [17–19].

2. Immunoregulatory genes to counteract the immune response that destroys β cells, such as interleukin-1 receptor antagonist protein (IRAP), interleukin (IL)-10, IL-4, the chemokine CCL22, US2 protein of human cytomegalovirus, serpin-9, and transforming growth factor β (TGF-β) [20–23].

3. Factors that promote vascularization, such as HGF and vascular endothelial growth factor (VEGF), given that hypovascularization, hypoxia, and nutrient deprivation have been deemed likely culprits for the short-term survival of transplanted islets [24, 25].

In general, these strategies have enhanced the viability and function of the transplanted islets and attenuated β-cell death, preventing graft failure and reversing hyperglycaemia. In addition to the *ex vivo* genetic manipulation of islets, AAV vectors have been used *in vivo* to deliver immunomodulatory genes, such as the immunosuppressive IL-10 or Epstein–Barr–derived BCRF-1, to the muscle of the recipient of the islet graft prior to the transplant [26, 27].

Table 78.1 General characteristics of the most commonly used viral vectors.

Viral vector	Retroviral (RV)	Lentiviral (LV)	Adenoviral (Ad)	Adeno-associated (AAV)	Herpes simplex (HSV)
Family	*Retroviridae*	*Retroviridae*	*Adenoviridae*	*Parvoviridae*	*Herpesviridae*
Pathogenicity of parental virus	Yes	Yes	Yes	No	Yes
Genome	ssRNA, lineal	ssRNA, lineal	dsDNA, lineal	ssDNA, lineal	dsDNA, lineal
Maximum cloning capacity	8 kb	8 kb	36 kb	4.7 kb	150 kb
Production at high titres	Yes	No	Yes (lower titres with third-generation vectors)	Yes	No
Insertion in host genome	Yes, with preference for regulatory elements	Yes, but with no preference for regulatory elements	No	Yes, but randomly and with extremely low frequency, mainly episomal	No
Innate immunity	Yes	Yes	High for first- and second-generation vectors	Very limited	Yes
Target cells	Infects dividing cells	Infects dividing and quiescent cells	Infects dividing and quiescent cells	Infects dividing and quiescent cells	Infects dividing and quiescent cells
Transgene expression	Long-lasting	Long lasting	Short-lived, except for third-generation vectors	Long-lasting	Short-lived, except for late-generation vectors
Main advantages	Long-lasting expression in dividing cells Production at high titres	Long-lasting expression in dividing cells	Episomal Production at high titres (except for third generation) High levels of transduction *in vivo* High cloning capacity	Episomal Production at high titres High levels of transduction *in vivo* Non-pathogenic, low immunogenicity Several serotypes with different tissue tropism	Episomal High cloning capacity
Main disadvantages	Infects only dividing cells Limited cloning capacity Risk of insertional mutagenesis	Limited cloning capacity Risk of insertional mutagenesis, but lower than for retroviral vectors	Inflammatory and immune responses to the viral proteins limit persistence of transgene expression. Diminished in third-generation vectors Useful only for short-term studies Unselective tropism	Limited cloning capacity	Transient expression of the transgene Non-characterized neurotoxicity

This strategy prevents recurrence of autoimmunity and allogeneic rejection, resulting in prolongation of graft survival and remission of diabetes in mice [26, 27].

Ectopic production of insulin by non-β cells

Other gene therapy strategies have focused on the use of surrogate cells to produce insulin. In β cells, proinsulin is processed into mature insulin by the proprotein convertases PC1/3 and PC2, which are absent in the majority of other cells. To solve this problem and enable the processing of proinsulin by surrogate cells not expressing PC1/3 and PC2, new proteolytic sites have been engineered in the proinsulin molecule, which are recognized by furin, a protease present in most cells. Several cell types have been used in *ex vivo* gene transfer approaches to achieve ectopic production of insulin [28–44]. However, in most of these studies the therapeutic effect was short-lived due to loss of transplanted cells.

The most noteworthy results in the attempts to achieve ectopic insulin production have been obtained by genetic engineering of hepatocytes *in vivo*. Hepatocytes are attractive target cells because they express the same glucose-sensing molecules as β cells, such as the glucose transporter type 2 (GLUT2), which mediates the insulin-independent entry of blood glucose into the cell, and the enzyme glucokinase (GK), which phosphorylates the incoming glucose molecule. In addition, hepatocytes are essential regulators of carbohydrate metabolism and several genes expressed in the liver are transcriptionally regulated by glucose or insulin, offering the possibility of engineering glucose/insulin-controlled expression cassettes that mediate the production of insulin as a function of circulating glucose and insulin levels. To this end, naturally occurring promoters such as those from the GLUT2, phosphoenolpyruvate carboxykinase (PEPCK), glucose-6-phosphatase (G-6-Pase), and liver-pyruvate kinase (L-PK) genes as well as engineered hybrid and synthetic promoters have been used to mediate glucose/insulin-responsive insulin expression following *in vivo* delivery of gene transfer vectors [45–53]. Furthermore, lentiviral- and AAV-mediated constitutive expression of insulin by hepatocytes has been reported to be efficacious in diabetic rodents [41, 54–56]. However, none of the aforementioned *in vivo* systems managed to mimic the quick response to glucose of the insulin promoter [34], and the slow glucose-mediated transcriptional control of these promoters may result in an inadequate insulin secretory response, with postprandial episodes of hyperglycaemia followed by hypoglycaemia several hours later [48, 53, 57].

Enhancement of glucose disposal

As an alternative to ectopic insulin expression in the liver, transfer of the insulin gene can be used to engineer a glucose sensor in skeletal muscle to enhance glucose uptake in a glucose-dependent manner in this tissue to lower hyperglycaemia [58]. Several reasons support the choice of skeletal muscle as a target organ for this strategy. First, muscle can efficiently secrete proteins into the bloodstream and has a metabolism highly based on glucose consumption, accounting for ~70% of glucose disposal after a meal. Second, muscle is easily accessible by non-invasive procedures, and gene transfer by AAV vectors leads to minimal systemic biodistribution, limiting biological effects to this organ even if ubiquitous promoters are used to direct therapeutic transgene expression [59]. Moreover, gene delivery to muscle is not limited by the presence of pre-existing neutralizing antibodies against AAV [60], a key aspect given the relatively high prevalence of anti-AAV antibodies in the general population [61].

Under normal conditions, insulin stimulates glucose uptake in skeletal muscle by promoting the translocation of the glucose transporter type 4 (GLUT4) to the plasma membrane [62]. Once inside the muscle cell, glucose is phosphorylated by hexokinase II (HK-II) [63]. HK-II has a low Km for glucose and is inhibited by glucose-6-phosphate, which limits glucose uptake. In contrast to HK-II, the hepatic GK has a high Km for glucose (about 8 mM), is not inhibited by glucose 6-phosphate, and shows kinetic cooperativity with glucose [63]. In diabetes, because of the lack of insulin, the translocation of GLUT4 to the plasma membrane and mRNA levels and activity of HKII are decreased in muscle cells [64, 65], compromising the ability of the skeletal muscle to dispose of glucose after a meal. To counteract the hyperglycaemia, a novel gene therapy approach has been developed based on the co-expression of the insulin and glucokinase genes in muscle cells. The rationale behind this approach is based on the following premises:

- Expression of constant, low levels of insulin ensures translocation of GLUT4 to the plasma membrane without the risk of causing hypoglycaemia.
- Low levels of insulin are also sufficient to inhibit lipolysis and prevent ketoacidosis.
- The expression of GK draws the uptake of glucose into the muscle cell only when blood glucose levels are high.

Hence, the combination of these two genes generates a glucose sensor in the skeletal muscle that uptakes large quantities of glucose only when circulating glucose levels rise, such as in post-prandial conditions, but does not cause hypoglycaemia, because GK activity is shut down at physiological glucose concentrations.

As a proof of concept, this approach was first tested in transgenic animals that overexpressed the insulin and glucokinase genes specifically in skeletal muscle [58]. When rendered diabetic, these mice were normoglycaemic and did not develop secondary complications. Afterwards, AAV1 vectors were used to transfer the insulin and glucokinase (GCK) genes to the skeletal muscle of diabetic mice. In contrast to untreated diabetic mice, in AAV1-Ins- and AAV1-GCK-treated mice, long-term restoration of fed and fasted normoglycaemia was achieved [58]. AAV1-treated mice also showed increased skeletal muscle glucose uptake, normalization of glucose metabolism in the liver (increased glucose uptake and glycogen synthesis and reduced hepatic glucose production), and improved glucose tolerance [38]. Moreover, these mice had normal food and fluid intake, and the weight of the abdominal fat pad and skeletal muscle was normalized [58]. This study established the proof of concept that a gene therapy based on the production of basal levels of insulin and the increased uptake of glucose by the skeletal muscle allowed for tight regulation of glycaemia [58].

As a next step towards the clinical translation of this approach, a pre-clinical study in diabetic dogs was undertaken to investigate the feasibility, efficacy, and duration of the therapeutic effect as well as safety issues. A single intramuscular administration of AAV1 vectors encoding for insulin and GCK resulted in normalization of fasting glycaemia and accelerated disposal of glucose after an oral challenge for >4 years after gene transfer, with no episodes of hypoglycaemia, not even during exercise [59]. This normalization of glucose metabolism was associated with recovery of body weight, normal levels of glycated plasma proteins, and long-term survival without secondary complications. In contrast, gene transfer of either the insulin or the GCK genes alone failed to achieve complete correction of diabetes, indicating that a synergistic action of insulin and GK is needed for full therapeutic effect [59]. In a follow-up study, successful, multiyear (>8 yr) control of glycaemia without the need of supplementation with exogenous insulin was reported [66]. Metabolic correction was demonstrated through normalization of serum levels of fructosamine, triglycerides, and cholesterol, and remarkable improvement in the response to an oral glucose challenge. The persistence of vector genomes and therapeutic transgene expression years after vector delivery was documented in multiple samples from treated muscles, which showed normal morphology. This study demonstrated the long-term efficacy and safety of insulin and glucokinase gene transfer in large animals, and especially the ability of the system to respond to the changes in metabolic needs as animals grow older [66].

Reprogramming of surrogate cells into β cells

The concept of β-cell reprogramming implies the transdifferentiation of a surrogate cell into a functional β cell capable of sensing glucose and releasing insulin accordingly. This is generally achieved through the use of transcription factors, which are key for the differentiation of progenitor cells into β cells during pancreas development.

Most *in vivo* approaches tested so far have used adenoviral- or AAV-mediated gene transfer of pancreatic duodenal homeobox-1 (Pdx-1), NeuroD, MafA, and neurogenin-3 (Ngn3), individually or in combination, to liver or pancreatic cells [67–78]. Although adenoviral vectors generally mediate short-term expression of transgenes of interest (Table 78.1), their use here is justified because, at least in the liver of mice, adenoviral transduction *per se* is required for efficacy [77]. When the target cells were hepatocytes, oval cells, or ductal cells in the liver, hyperglycaemia partially ameliorated because of the expression of insulin in these cells, but full phenotypic conversion into functional β cells could not be achieved [67, 68, 71–74, 76, 77]. In contrast, when cells from the exocrine pancreas were reprogrammed, the resulting cells did not exhibit a hybrid or mixed phenotype, but closely resembled islet β cells at a biochemical and ultrastructural level [75, 78]. Furthermore, reprogrammed cells formed islet-like structures and mediated long-term (>1 yr) normalization of hyperglycaemia [75].

Promising results have also been obtained on reprogramming of α cells into functional β cells by adenoviral- or AAV-mediated expression of Pdx1 and MafA [70, 79]. The reprogrammed mouse insulin$^+$ cells exhibited a gene expression pattern similar to endogenous β cells and mediated normalization of glycaemia for four months in both alloxan-induced diabetic mice and non-obese diabetic (NOD) mice, a model of spontaneous autoimmune diabetes [70, 79]. These gene therapy strategies also induced α- to β-cell

conversion in both streptozotocin-treated human islets and purified human α cells before pseudo-islet reaggregation [70, 79]. When transplanted into immunodeficient NOD mice, reprogrammed cells ameliorated hyperglycaemia and glucose tolerance for at least six months [70, 79]. Pseudo-islets obtained on reaggregation of reprogrammed human α cells displayed a transcriptomic and proteomic signature that was intermediate between α and β cells, which further shifted towards that of β cells after transplantation into mice, and displayed reduced immunogenicity for type 1 diabetes autoreactive T cells [79]. Moreover, adenoviral-mediated expression of Pdx1 and MafA also mediated successful reprogramming of human γ cells, which produced and secreted insulin in response to glucose [79].

It should be borne in mind that *in vivo* and *ex vivo* genetically reprogrammed β cells, like endogenous islet β cells, will be susceptible to autoimmunity [70, 80], hence reprogramming gene therapy approaches may require concomitant immunotherapy to avoid destruction of the β-cell surrogates.

In Vivo β-cell regeneration

Another approach to restore the β-cell mass considers the regeneration of β cells from those cells that have survived the attack of the immune system. The regenerative potential of the endocrine pancreas seems to be quite high immediately after the onset of the disease [81], but it slows down as the disease progresses [82]. To induce replication of the remaining β cells, genes have been transferred *in vivo* to murine and canine β cells, mostly by means of adenoviral and AAV vectors, the latter having a much more efficient transduction, via different routes of delivery including intravenous and intraperitoneal systemic administration and local delivery to the pancreas through the bile-pancreatic duct [83–87]. Moreover, non-viral gene transfer to the pancreas in rats and non-human primates has also been reported using ultrasound targeted microbubble destruction technology (UTMD), although transgene expression was transient [88–90]. *In vivo* gene transfer of mitogenic and anti-apoptotic/pro-survival factors such as HGF, Sirtuin 1, angiopoietin-like protein 8, or downregulation of NADPH oxidase 2 (Nox2) or miR-338-3p reduced apoptosis and induced proliferation of β cells [85, 91–94]. Noticeably, delivery of glucagon-like peptide 1 (GLP-1), β-cellullin, Akt, or Nkx2.2 mediated not only β-cell regeneration but also reversal of diabetes [89, 95–98]. Other genes that promote therapeutic benefit in transgenic animal models and are therefore promising for gene therapy approaches for type 1 diabetes include insulin-like growth factor I (IGF-I), regenerating gene 1 (Reg1), epidermal growth factor (EGF), gastrin, and nerve growth factor (NGF) [99–103]. In this regard, AAV-mediated pancreatic-specific overexpression of IGF-I in NOD mice dramatically reduced diabetes incidence, both when vectors were delivered before pathology onset and once insulitis was established [104]. Treated NOD animals showed decreased β-cell apoptosis, preserved β-cell mass, normal insulinaemia, and lower islet infiltration than controls. Moreover, AAV-IGF-I-treated NOD mice also exhibited decreased islet expression of antigen-presenting molecules, inflammatory cytokines, and chemokines important for tissue-specific homing of effector T cells, suggesting IGF-I modulated islet autoimmunity [104].

Immune modulation

The immune system is a key component of the aetiopathogenesis of type 1 diabetes. The T cell–mediated destruction of β cells arises as a consequence of the breakage of tolerance to β-cell antigens. Consequently, many gene therapy approaches developed for the treatment of type 1 diabetes aim to increase the number and/or activation of regulatory T cells (Tregs) and/or decrease the frequency of autoreactive T cells. Among all vectors, AAVs have been the most widely used vectors *in vivo* to transfer immunomodulatory genes to prevent or ameliorate type 1 diabetes in mice. AAV-mediated overexpression of the cytokines IL-2, IL-4, IL-10, IL-35, or the chemokine CCL22 have demonstrated therapeutic efficacy in NOD mice [105–111]. IL-2 is the key cytokine supporting the survival and function of Tregs [105]. Treatment with low-dose recombinant IL-2 safely expands and stimulates Tregs and improves the clinical condition in humans with type 1 diabetes, but multiple administrations were needed [112]. In contrast, one-time, AAV-mediated, systemic, muscular, or β cell–specific delivery of the IL-2 gene increased the frequency and activation of Tregs and prevented diabetes in NOD mice [105, 106, 108]. IL-4 induces the expression of the transcription factor forkhead box P3 (Foxp3), the defining marker of Tregs [113], in Treg precursor cells [114]. AAV-mediated expression of IL-4 in β cells prevented islet destruction and onset of diabetes in NOD mice [110].

On the other hand, IL-10 plays an important role in the development of Tregs and secretion of IL-10 by Tregs inhibits effector T-cell responses [113]. Gene transfer of IL-10 to murine muscle increased Tregs in a dose-dependent manner and abrogated diabetes development [107]. IL-35 is secreted by and contributes to the suppressor function of Tregs [115]. Additionally, IL-35 promotes differentiation of $CD4^+$ T cells into induced regulatory Th35 suppressor cells [116]. AAV-mediated β cell–specific expression of IL-35 in NOD mice suppressed β-cell autoimmunity and prevented diabetes onset. Protection was marked by significantly reduced numbers of islet $CD4^+$ and $CD8^+$ T cells and dendritic cells and a phenotypically distinct islet $Foxp3^+$ Treg pool, which in turn was needed to suppress effector $CD4^+$ T differentiation [111]. Finally, CCL22 is the ligand of the chemokine receptor CCR4, highly expressed on Tregs. Overexpression of CCL22 in β cells recruited endogenous Tregs to the islets, limiting the expansion and effector activity of autoreactive T cells and conferring long-term protection from autoimmune diabetes [109].

Another strategy is based on the conversion of cytotoxic T cells, including pathogenic, β cells pecific T cells, into Tregs through *ex vivo* lentiviral or retroviral vector-mediated gene transfer of Foxp3 [117, 118]. Tregs have also been genetically engineered with antigen-specific immunoreceptors using lentiviral vectors to generate islet-specific Tregs, which showed antigen-specific suppression *in vitro* and compare favourably to adoptive Treg therapy using *ex vivo* expanded polyclonal Tregs [119]. Polyclonal Tregs therapy is currently in clinical trials for the treatment of type 1 diabetes [120], but antigen-specific Tregs exhibit higher specific potency, furthering the promise of this therapy [119]. In addition, systemic administration of adenoviral vectors encoding a cytotoxic T lymphocyte–associated antigen 4 (CTLA4)-Fas ligand fusion protein stimulated apoptosis, blocked co-stimulation of autoreactive T cells, and greatly reduced the incidence of type 1 diabetes [121]. *Ex vivo* antigen-specific targeting of autoreactive CD8 or CD4 T cells specifically killed diabetogenic T cells *in vitro* as well as reducing the incidence and delaying the onset of diabetes in NOD mice [122, 123]. Similarly, engineered CAR-T cells that specifically target diabetogenic APCs delay the onset of type 1 diabetes in NOD diabetes [124].

Another group of strategies has relied on the active induction of immune tolerance, for example by expression of the pre-proinsulin

II gene in the thymus following intrathymic administration of lentiviral vectors [125]; by non-viral, lentiviral, or AAV-mediated gene transfer of the IGF-I gene, the insulin B chain 9–23 (InsB9–23), or the major histocompatibility complex (MHC) class I molecule H-2K to the liver [126–129]; or by transient, adenoviral-mediated expression of a soluble form of the immunoadhesin intercellular adhesion molecule 1 (ICAM-1) [130] soon after diabetes onset. All these approaches resulted in suppression of autoimmune diabetes in NOD mice or transgenic mice overexpressing human interferon β in β cells [100], both of which are murine models of human type 1 diabetes. Induction of antigen-specific tolerance by retroviral-mediated expression of insulin or glutamic acid decarboxylase 65 (GAD65) in B lymphocytes is also promising for type 1 diabetes [131]. Likewise, the administration of viral vector- or plasmid-based gene transfer vaccines encoding the autoreactive antigens insulin, proinsulin, or GAD65 induces immune tolerance and prevents the development of type 1 diabetes in mice [132–134].

Gene therapy for type 2 diabetes

Although most of the gene therapy strategies developed so far for diabetes have focused on type 1 diabetes, as the scientific understanding of the pathophysiology of type 2 diabetes increases, a growing number of proof-of-concept gene transfer studies are being conducted in rodents to evaluate the therapeutic efficacy of several candidate factors, as well as to gain insight into the molecular mechanisms underlying type 2 diabetes. The results of these studies highlight the tremendous potential of the genetic modification of metabolic tissues for the treatment of type 2 diabetes.

Type 2 diabetes results from a state of insulin resistance in peripheral tissues (mainly skeletal muscle, adipose tissue, and liver), which is not appropriately compensated for by an increased insulin secretory response, likely due to a combination of decreased β-cell mass and function. Development of insulin resistance and type 2 diabetes is strongly associated with obesity. Obesity results from a sustained imbalance between energy intake and expenditure. Indeed, impaired brown adipose tissue (BAT) activity (non-shivering thermogenesis) and/or decreased mass are considered among the main contributors to type 2 diabetes and obesity both in experimental animal models and in humans.

Therefore, the vast majority of gene therapy strategies for type 2 diabetes have focused on ameliorating insulin resistance and glucose tolerance, on enhancing energy expenditure (by increasing BAT activity and/or inducing browning of white adipose tissue [WAT]), and on improving adipose tissue dysfunction and inflammation.

Amelioration of insulin resistance

The systemic administration of adenoviral vectors encoding GLP-1 improved insulin sensitivity through restoration of insulin signalling in peripheral tissues and reduction of hepatic gluconeogenesis in diabetic obese *ob/ob* mice [135]. The attenuation of insulin resistance has also been achieved in type 2 diabetes high-fat diet (HFD)-fed rats through systemic AAV-mediated gene transfer of the serine protease kallikrein [136]. Kallikrein converts kininogen to the peptidic hormone bradykinin, which increases insulin sensitivity and stimulates glucose uptake *in vivo* [137]. Similarly, the AAV-mediated local gene transfer of HK-II to WAT or BAT has managed to increase glucose uptake in adipocytes [138, 139], and may also be a promising strategy for improving insulin sensitivity in type 2 diabetes [140]. Intra-WAT administration of AAV vectors encoding perilipin A reduced blood glucose and free fatty acid levels and modified the respiratory exchange ratio, indicating a more pronounced use of glucose as an energy source [141].

Individuals with type 2 diabetes overexpress phosphoprotein enriched in diabetes/phosphoprotein enriched in astrocytes (PED/PEA-15) in skeletal muscle and adipose tissue [142], a protein that causes insulin resistance by interacting with the D4 domain of phospholipase D1 (PLD1) [143]. The disruption of the association between PLD1 and PED/PEA-15 at a tissue level through adenoviral-mediated overexpression of a soluble form of D4 in the liver, pancreas, and skeletal muscle restored glucose homeostasis by improving both insulin sensitivity and secretion in diabetic transgenic mice ubiquitously overexpressing PED/PEA-15 and in obese HFD-fed wild-type mice [144].

Cholesterol is involved in the development of obesity, insulin resistance, and hepatic steatosis [145]. The ABCG5 ABCG8 (G5G8) sterol transporter promotes cholesterol excretion into the bile and the intestinal lumen. Following adenovirus-mediated delivery of the G5G8 genes to the liver of *db/db* mice, the levels of biliary cholesterol and faecal sterol increased, the levels of plasma glucose and triglycerides decreased, and glucose tolerance improved [145]. These changes were associated with reduced expression of lipogenic genes, alleviation of endoplasmic reticulum (ER) stress, and restoration of hepatic insulin signalling [145].

Expression and activity of HO-1 are reduced in obesity, resulting in elevation of reactive oxygen species and insulin resistance in both humans and mice [146]. Adipose-specific lentiviral-mediated overexpression of HO-1 in HFD mice increased insulin sensitivity in adipose tissue, and decreased adipocyte hypertrophy and expression of inflammatory cytokines and fibrosis in WAT. Moreover, HO-1–treated mice also showed increased thermogenesis, reduced body weight and fasting blood glucose levels, and increased glucose tolerance [146].

Enhancement of thermogenesis and reduction of adipose tissue dysfunction and inflammation

Given the strong association between type 2 diabetes and obesity, many gene transfer studies have targeted adiposity, adipocyte dysfunction, and/or adipose tissue inflammation as well as energy expenditure, with the aim of ultimately improving insulin sensitivity and glucose tolerance. AAV-mediated gene transfer of bone morphogenic protein 4 (BMP4) to the liver of mice resulted in increased BMP4 circulating levels and enhanced whole-body energy expenditure due to marked browning of WAT. AAV-BMP4–treated mice were protected from obesity and showed improved insulin sensitivity and glucose tolerance [147]. In obese animals, AAV-BMP4 vectors had no effect on body weight, browning of WAT, or energy expenditure, but whole-body insulin sensitivity and glucose tolerance were robustly improved [148]. Insulin signalling and insulin-stimulated glucose uptake were increased in both adipose cells and skeletal muscle. AAV-BMP4 also decreased hepatic glucose production, reduced gluconeogenic enzymes in the liver, and enhanced insulin action [148].

Several studies have shown that cold temperature can activate pro-opiomelanocortin-expressing neurons and increase sympathetic neuronal tone to regulate browning of WAT. AAV-mediated overexpression of connexin 43 in white adipocytes mediated browning of WAT by facilitating the propagation of sympathetic neuronal signals [149]. Likewise, AAV-mediated BAT-specific miR-32 overexpression led to increased BAT thermogenesis and browning of WAT [150]. The intra-cerebroventricular administration of AAV vectors encoding the adipokine leptin prevented

HFD-induced adiposity, reduced blood glucose and insulin levels, and increased thermogenesis [151]. The effect was mediated by transduction of the hypothalamic cells of the brain [152]. Intraperitoneal or intra-WAT administration of AAV-leptin vectors to *ob/ob* obese mice also mediated therapeutic benefit, ranging from partial to total, in ameliorating obesity and glucose homeostasis [153, 154]. The administration to the skeletal muscle of AAV vectors encoding the secreted glycoprotein Wnt10b, a recently described member of the Wnt family reported to inhibit adipogenesis, decreased overall fat mass and improved glucose and energy homeostasis in obese rats [155]. In humans, mutations in Wnt10b are associated with obesity [156], and certain variants of the transcription factor 7-like 2 (*TCF7L2*, formerly *TCF4*) gene, another member of the Wnt signalling pathway, confer increased risk of type 2 diabetes [157].

AAV-mediated delivery to white adipocytes of mitoNEET, a protein residing in the mitochondrial outer membrane and involved in the regulation of mitochondrial iron content, or of BMP7 resulted in benign expansion of WAT, reduced inflammation, and preservation of insulin sensitivity in obese mice [158, 159]. Likewise, the adenoviral-mediated gene transfer of the secreted frizzled-related protein 5 (Sfrp5) to the liver reduced adiposity and adipose tissue inflammation in different models of obesity and diabetes, improving glucose tolerance and insulin sensitivity [160]. Sfrp5 is an anti-inflammatory adipokine linked to the Wnt signalling pathway whose expression is perturbed in models of obesity and type 2 diabetes [160]. Inhibition of macrophage infiltration and inflammation in adipose tissue occurs on intravascular delivery to obese diabetic mice of adenoviral vectors encoding GLP-1 that result in increased circulating levels of the protein [161]. This observation suggested that the anti-inflammatory action of GLP-1 on adipose tissue might be the mechanism underlying the reported improvement in insulin sensitivity.

Interferon regulatory factor (IRF) proteins are a family of nine transcription factors involved in the mammalian regulation of type I interferon expression and innate immunity [162, 163]. These proteins also seem to play an important role in metabolism [164, 165]. For example, hepatic expression of IRF3 decreases in animals with diet-induced and genetic obesity [165], making IRF proteins interesting targets for gene therapy approaches to counteract type 2 diabetes. Adenoviral-mediated liver-specific overexpression of IRF3 or 9 improves glucose and lipid homeostasis and attenuates systemic and hepatic inflammation in diet-induced diabetic and *ob/ob* mice [164, 165].

Another promising therapeutic candidate for type 2 diabetes and obesity is adiponectin, which possesses insulin-sensitizing and anti-inflammatory properties [166]. In humans, adiponectin levels are inversely correlated with the degree of adiposity, insulin resistance, and type 2 diabetes [167, 168]. Muscular or hepatic gene transfer of adiponectin by means of AAV vectors enhanced insulin sensitivity, reduced obesity, and downregulated hepatic gluconeogenesis, *de novo* lipogenesis, and inflammation in HFD-fed diabetic rats [166, 169]. Similar results were obtained on non-viral-mediated overexpression of adiponectin in obese-diabetic rats [170]. Likewise, the adenoviral-mediated expression of C1q/TNF-related protein-12, an adipokine sharing partial homology with adiponectin, improved glucose tolerance and insulin sensitivity, and normalized hyperglycaemia and hyperinsulinemia in obese diabetic mice [171].

Obesity-associated adipose tissue hypoxia that occurs as a result of insufficient blood flow could trigger insulin resistance by inducing inflammation, altering adipokine expression, and/or affecting adipocyte differentiation [172–174]. Recent studies have demonstrated that AAV-mediated overexpression of VEGF in murine WAT or BAT can not only increase tissue vascularization, but also induce browning of WAT or non-shivering thermogenesis in BAT, respectively [138, 175, 176]. This may be a promising approach for the treatment of type 2 diabetes, as VEGF overexpression in adipose tissue of transgenic mice protects against obesity and insulin resistance in HFD-fed mice [177].

Long-term reversal of insulin resistance and obesity

Although the aforementioned gene transfer approaches for insulin resistance and obesity show promising results in animal models, long-term therapeutic benefit has not been reported for any of them.

Fibroblast growth factor 21 (FGF21) has recently emerged as a promising therapeutic agent for the treatment of type 2 diabetes and metabolic disorders [178, 179]. This peptide hormone is secreted by several organs and can act on multiple tissues to regulate energy homeostasis. FGF21 analogues with improved pharmacokinetic properties have reached the clinical stage, and reports from phase I and phase II clinical trials have shown significant improvement of dyslipidaemia, slight body weight loss, increases in adiponectin, and reductions in fasting insulinaemia in individuals with obesity and type 2 diabetes [180–186]. Nevertheless, engineered FGF21 mimetics or analogues may raise immunological issues associated with the administration of exogenous proteins [180–182, 187, 188]. In contrast, gene therapy allows one to work with the wild-type protein that is recognized as its own by the immune system and signals through the canonical FGF21 signalling pathways, avoiding unspecific biological responses.

Recently, a single administration of AAV vectors encoding native FGF21 was reported to enable efficient genetic engineering of the liver and long-lasting secretion of therapeutically relevant levels of FGF21 to the bloodstream, which mediated sustained (>1 yr) counteraction of obesity, non-alcoholic steatohepatitis (NASH), and insulin resistance in two different models of obesity and type 2 diabetes (HFD-fed mice and *ob/ob* mice) [189]. Specifically, reversal of adipose tissue hypertrophy and inflammation as well as of hepatic steatosis, inflammation, and fibrosis was achieved. Moreover, AAV-FGF21–based gene therapy also mediated improvements in energy expenditure and glucose homeostasis, which were linked to increased non-shivering thermogenesis in BAT, glucose uptake in brown or white adipocytes, normalization of adiponectin and leptin levels, and counteraction of islet hyperplasia, with consequent reduced insulin and glucagon levels. These therapeutic effects were achieved in the absence of side effects despite continuously elevated serum FGF21. Indeed, AAV-FGF21–treated mice were protected from obesity-associated liver neoplasms. Similar therapeutic benefit was reproduced after genetic engineering of adipose tissue or skeletal muscle to mediate sustained FGF21 circulating levels [138, 189]. Furthermore, FGF21 overproduction in healthy animals fed a standard diet expanded health span and prevented age-related weight gain and insulin resistance, confirming that AAV-FGF21 gene therapy is safe [189].

Therefore, AAV-FGF21–based gene therapies recapitulate the previously reported benefits of pharmacological FGF21 analogues and mimetics, while avoiding essential obstacles such as treatment adherence and immunogenic reactions. These findings reinforce the therapeutic efficacy of AAV-mediated FGF21 gene therapy and constitute the basis to support the future clinical translation of FGF21 gene transfer to treat type 2 diabetes, obesity, and related comorbidities.

Conclusion and perspectives

Viral vectors have taken the lead as tools to achieve efficient *ex vivo* and *in vivo* long-term genetic modification of tissues and organs through a single vector delivery. This technological advance has opened the possibility not only of performing gene transfer studies to understand the role of a given gene in disease, but also of the development of new therapeutic strategies. In the case of diabetes there are several gene transfer approaches with demonstrated efficacy in lowering blood glucose that could offer an advantage over conventional treatments. Future studies are required to demonstrate the efficacy and safety in large animal models of the approaches that have demonstrated promise in small animals before any of these gene therapies are brought to the clinic to treat diabetes in humans.

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79 Future Drug Treatments for Type 2 Diabetes

Clifford J. Bailey
School of Life and Health Sciences, Aston University, Birmingham, UK

Key points

- Despite a variety of differently acting glucose-lowering agents, many people with type 2 diabetes do not achieve or maintain adequate glycaemic targets. Hence there is a continued need for new agents.
- The variable aetiology and pathogenesis of type 2 diabetes require a diversity of therapies that can be used in combination as the disease progresses.
- Fixed-ratio combinations of peptides such as a glucagon-like peptide 1 (GLP-1) receptor agonist with insulin, and potential hybrid peptides of incretins and other gluco-regulatory hormones, offer the opportunity to interact with several target receptors via a single injection.
- Further incretin-based therapies include orally active peptide formulations, small-molecule (non-peptide) receptor agonists, and depot injections.
- Tissue selective insulins and glucose-responsive (smart) insulins are attractive possibilities: the latter release insulin from a circulating chemical complex or implanted depot by direct chemical interaction with glucose, so that rising concentrations of glucose are matched by increasing release of insulin.
- Novel insulinotropic agents have been shown to alter β-cell energetics, reduce β-cell apoptosis, and preserve β-cell mass in pre-clinical studies: these could slow the long-term progression of type 2 diabetes.
- Proof of principle has been demonstrated for small molecules to mimic and potentiate insulin action to counter insulin resistance.
- Glucagon receptor antagonists, selective peroxisome proliferator-activated receptor (PPAR) modulators, cellular glucocorticoid inhibitors, adiponectin receptor agonists, and fibroblast growth factor analogues continue to be at various stages of development.
- Agents that directly enhance glucose metabolism or suppress glucose production have been described, such as activators of adenosine 5′-monophosphate-activated protein kinase.
- New inhibitors of sodium–glucose cotransporters (SGLT-1 and SGLT-2) are becoming available.
- Emerging pharmacogenomics and proteomics could offer novel therapeutic opportunities.

Despite many initiatives to prevent type 2 diabetes, its prevalence continues to rise, accounting for >90% of the global totality of people with diabetes (~465 million in 2019 and projected to be ~700 million by 2045) [1]. Current treatment strategies are reviewed in earlier chapters of this book, and the importance of an early, effective, individualized therapeutic approach to glycaemic management is emphasized to defer the onset and reduce the severity of complications. Although many differently acting classes of glucose-lowering agents are already available (Figure 79.1), a sustained return to normal glucose homeostasis is rarely achieved, and more than one-third of people with type 2 diabetes do not attain or maintain acceptable glycaemic targets [2–4]. This chapter reviews some of the new therapeutic approaches under consideration to improve glycaemic management in type 2 diabetes, from innovative concepts in pre-clinical investigation through to agents advanced in clinical development.

Development of new glucose-lowering agents

The highly variable aetiology and pathogenesis of type 2 diabetes, which typically involves disturbances in multiple tissues and organ systems, open the possibility of many potential approaches to blood glucose management [5]. Some of these approaches directly target underlying pathophysiological defects such as insulin resistance and pancreatic β-cell dysfunction, but interventions that improve glycaemic indices by any safe means should reduce the risk of complications. Because treatments are often life-long and contemporaneous with comorbidities, frailty, multiple pharmacotherapies, and lifestyle challenges, it is important that new agents offer a commendable safety profile, are well tolerated, and are compatible with a broad selection of other medications. Ideally, they will provide durable and additive glucose-lowering efficacy to existing agents through different but complementary modes of action, while carrying minimal risk of serious hypoglycaemia. Additional capability to reduce adiposity and improve other modifiable cardiovascular risk factors such as dyslipidaemia and hypertension would also be preferred.

Identifying a new chemical entity and progressing it through the pre-clinical and clinical phases of development to marketing approval are likely to take at least 10 years (Table 79.1). The cost is expected to exceed US$1 billion, with some estimates up to US$2.8 billion [6]. For glucose-lowering drugs, post-authorization safety studies to monitor cardiovascular outcomes and other events may be required [7]. Further development is often undertaken for additional indications and to produce new formulations, including single-tablet fixed-dose combinations or fixed-ratio injection combinations.

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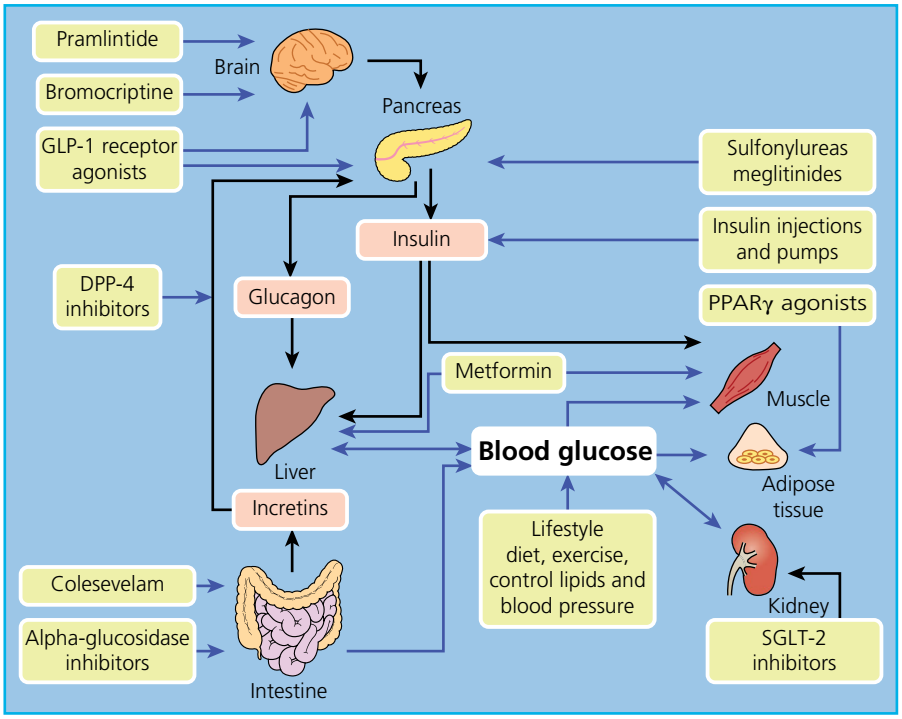

Figure 79.1 Current glucose-lowering therapies showing their main sites of action. Not all classes of therapies are indicated for the treatment of type 2 diabetes in all regions. DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide 1; PPAR, peroxisome proliferator-activated receptor; SGLT-2, sodium–glucose cotransporter 2.

Table 79.1 Stages in the development of a new drug.

Pre-clinical stages
New chemical entity
• Identification, extraction/synthesis, chemical characterization, and patenting of compounds
• Genotoxicity testing: screening for biological activity *in vitro* and *in vivo* in animals
• Pre-clinical pharmacology, mode of action, pharmacodynamics (activity, safety, tolerance), pharmacokinetics (bioavailability, distribution, metabolism, elimination), and toxicity in ≥2 mammalian species
Clinical stages
Investigational new drug application: permission to begin clinical studies
Phase I
• First administration to a small number of healthy human volunteers
• Dose ranging, vital signs, pharmacodynamics, pharmacokinetics, drug interactions, safety
Phase II
• First trials in small numbers of people with the condition
• Dose ranging, efficacy, further pharmacodynamics, pharmacokinetics, and safety
Phase III
• Trials in larger numbers of people with the condition
• Multicentre trials, comparative trials with other treatments, efficacy, further pharmacodynamics and safety (including meta-analysis of cardiovascular events)
New drug application: permission to market as a drug
Phase IV
• Use in medical practice
• Additional trials (similar to phase III) for long-term efficacy and safety, and use in special subgroups (e.g. older people), post-marketing surveillance, and adverse drug reactions

Dietary supplements and intestinal agents

Of the many dietary supplements promoted as beneficial in type 2 diabetes, there are substantial data confirming that various soluble and insoluble plant polysaccharides can delay the digestion and absorption of carbohydrates, and may exert a prebiotic effect to alter the intestinal microbiome (Table 79.2). Reductions of post-prandial hyperglycaemia and *carry-over* reductions in basal glycaemia are generally modest, but can be useful when taken in conjunction with most classes of glucose-lowering pharmacotherapies [8]. Extended digestion times achieved with fibre supplements can reduce inter-prandial hypoglycaemia in insulin-treated individuals. Various changes in the composition of the intestinal microbiome have been reported in type 2 diabetes, and some probiotic cultures have been associated with modest glucose lowering in some studies, although findings have been inconsistent [9, 10].

The effects of vitamin and mineral supplements as adjunct treatments in type 2 diabetes remain controversial, and it is stressed that potential benefits of correcting deficiencies are very different to massive doses for individuals who already have adequate levels. Deficiencies in vitamin D are associated with insulin resistance and β-cell dysfunction, but supplementation in deficient individuals has shown only nominal (if any) reductions in glycated haemoglobin (HbA_{1c}) [11]. Low concentrations of antioxidant vitamins, notably vitamins C (ascorbic acid) and E (α-tocopherol) and β-carotene, are not uncommon in type 2 diabetes, but supplements have achieved little improvement in glycaemic indices or cardiovascular risk [12]. Thiamine (vitamin B_1) and biotin (vitamin H) have also been considered as possible supplements to improve glucose metabolism [13].

Reduced levels of magnesium, chromium, and zinc are frequently encountered in type 2 diabetes and supplements have

Table 79.2 Dietary fibre supplements and probiotics.

	Mechanisms of action	Effect on glycaemic indices
Soluble fibre e.g. gums, pectins, hemicelluloses, mucilages, fructans Insoluble fibre e.g. celluloses, wheat bran	Includes non-digestible carbohydrate and entrapped digestible carbohydrate causing digestion and absorption to be slowed. Possible prebiotic effect to alter microbiome	Reduce post-prandial hyperglycaemia: modest reductions of fasting plasma glucose and glycated haemoglobin (HbA_{1c})
Probiotics Live cultures of e.g. *Lactobacillus species* and *Bifidobacterium species*	Mechanisms unclear: probably decrease gut permeability, immunomodulation, increase short-chain fatty acid production	Small reductions in fasting plasma glucose and HbA_{1c} in some studies (considerable differences in cultures tested and study designs)

improved glycaemia in deficient individuals [14]. Selenium, molybdenum, tungsten, mercury, and cadmium have also been reported to improve glucose metabolism in pre-clinical models, but the mechanisms are unclear, the therapeutic index is generally narrow, and toxicity risks are high. Lithium can improve insulin sensitivity, but may also decrease insulin secretion with unpredictable effects [15].

Inhibitors of α-amylases to slow the hydrolysis of starch continue to generate interest, but have not given sufficiently predictable effects for therapeutic application [16]. Inhibitors of brush-border α-glucosidases such as acarbose, miglitol, and voglibose are well established therapies to slow the last stages of carbohydrate digestion. Although novel α-glucosidase-inhibiting molecules have been identified, these have not proceeded in clinical development [17]. Inhibition of sodium–glucose cotransporter 1 (SGLT-1) in the intestinal brush border provides another option to slow the absorption of glucose, and this is considered in a later section.

Supporting pancreatic β-cell function

Disturbances of pancreatic β-cell function occur early in the pathogenesis of type 2 diabetes and β-cell failure is a prominent feature of advanced stages of type 2 diabetes, making the β cell a key therapeutic target. Agents that initiate insulin secretion (sulfonylureas and meglitinides) or potentiate nutrient-induced insulin secretion (dipeptidyl peptidase 4 [DPP-4] inhibitors and glucagon-like peptide 1 [GLP-1] receptor agonists) are widely used in the treatment of type 2 diabetes (see Chapters 35 and 36). These agents partially compensate for the loss of an adequate first-phase insulin response in type 2 diabetes, enhance the second phase of secretion, and improve the secreted proportion of insulin relative to proinsulin. Limitations to the clinical use of these agents are considered in Chapter 35, but it is emphasized here that preservation or restoration of β-cell mass and function, especially in advanced stages of type 2 diabetes, remains a fundamental challenge [5].

Many compounds with insulin-releasing properties have received pre-clinical and early clinical investigation, but targeting the pancreatic β cells to the exclusion of other cell types has been a particular problem, and few compounds have proceeded further in development [15]. Included here are agents that increase adenosine triphosphate (ATP) production, close K^+ATP channels, depolarize the β-cell membrane, increase cytosolic calcium, enhance cyclic adenosine monophosphate (cAMP) or protein kinase C (PKC), activate imidazoline receptors, or suppress α_2-adrenergic receptors.

Glucokinase activators

Agents that activate the glucose phosphorylating enzyme glucokinase (GK) (EC 2.7.1.1) continue to attract interest as a means of initiating insulin secretion by increasing β-cell glucose metabolism (Figure 79.2). However, this approach is prone to precipitate hypoglycaemia and often incurs loss of efficacy after several months of treatment in type 2 diabetes [16, 17]. Glucokinase is also expressed in the liver, where it is regulated differently to pancreatic β cells. Hepato-selective GK activators are being investigated to increase post-prandial hepatic glucose uptake, and although this avoids hypoglycaemia, it presents a risk of excess glycogen deposition and increased lipogenesis in the liver.

Fatty acid receptor agonists

Pancreatic β cells express G protein–coupled receptors for medium-chain and long-chain free fatty acids, notably FFAR1 (GPR40) and GPR119. Small-molecule agonists of these receptors can enhance insulin secretion in different ways: FFAR1 agonists can initiate and potentiate insulin secretion via raised cytosolic Ca^{2+}; whereas GPR119 signals via adenylate cyclase to potentiate nutrient-induced insulin secretion by raising cAMP [18, 19] (Figure 79.2). Both FFAR1 and GPR119 are expressed by enteroendocrine K cells, L cells, and I cells; this enables agonists for these receptors to increase the incretin effect by increasing secretion of glucose-dependent insulinotropic peptide (GIP), GLP-1, and polypeptide YY (PYY), and further increasing satiety via oxyntomodulin and cholecystokinin. Activation of FFAR1 receptors expressed by pancreatic α cells may also reduce glucagon secretion, whereas GPR119 agonists can raise glucagon levels [20]. Agonists of another fatty acid receptor, FFAR4 (GPR120), which is widely expressed mainly by endocrine, intestinal, and adipose tissues, promote adipogenesis, increase insulin sensitivity, improve glucose tolerance, and reduce ectopic fat. FFAR4 is therefore being considered as a potential therapeutic target [21]. The widespread expression and diverse effects of fatty acid receptors, however, create challenges to confine the effects of agonists to selected tissues.

Imeglimin

Imeglimin is a triazine compound that alters mitochondrial energetics with an increased flux through complex III, and possibly also delays the opening of mitochondrial permeability transition pores. This increases ATP synthesis, reduces the production of reactive oxygen species, and restricts the release of pro-apoptotic proteins from mitochondria [22]. Accordingly, in pancreatic β cells glucose-stimulated insulin secretion is improved and apoptosis is reduced, while hepatic gluconeogenesis is suppressed and insulin-mediated glucose uptake by skeletal muscle is enhanced.

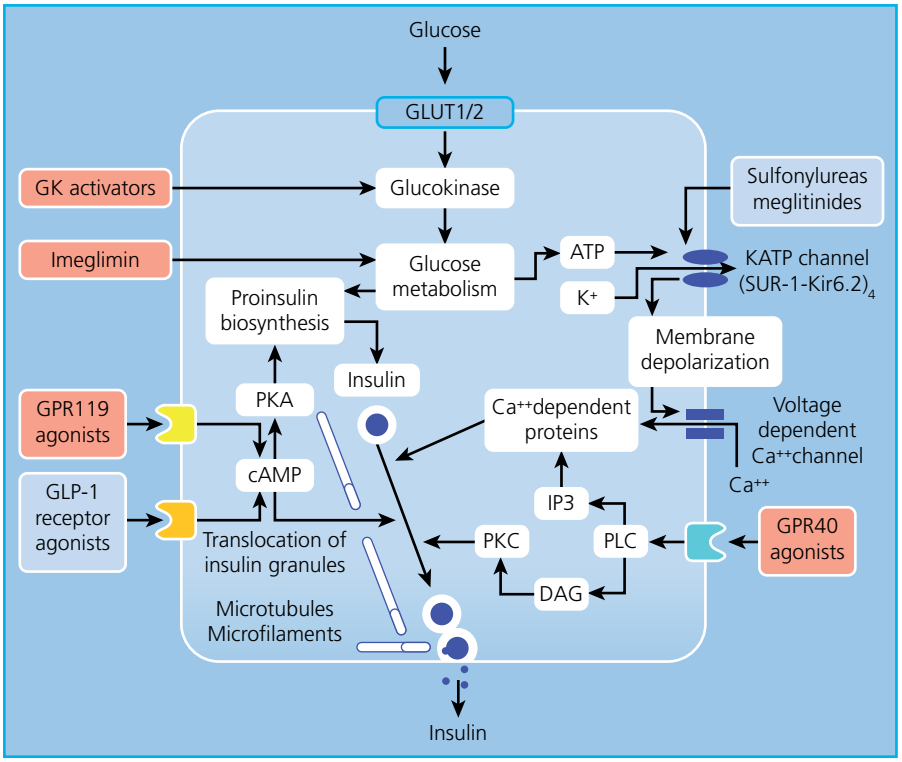

Figure 79.2 Mechanisms of action of insulin-releasing agents on pancreatic β cells. Glucose is taken up by the pancreatic β cells in proportion to the circulating concentration. The glucose is metabolized to produce adenosine triphosphate (ATP), which closes the Kir6.2 pores of ATP-sensitive potassium channels (K_{ATP} channels). This reduces elimination of potassium from the cell, causing localized membrane depolarization that opens voltage-dependent calcium channels. The influx of Ca^{2+} raises the cytosolic Ca^{2+} concentration, which activates calcium-dependent proteins that promote the translocation of insulin granules to the plasma membrane for exocytosis. Sulfonylureas and meglitinides initiate insulin release mainly by binding to sites on the sulfonylurea receptor 1 (SUR1), which forms part of the Kir6.2 complex. Activated glucagon-like peptide 1 (GLP-1) receptors and GPR119 receptors increase adenylate cyclase activity, which raises cyclic adenosine monophosphate (cAMP) concentrations, while FFAR1 (GPR40) receptor agonists are functionally linked to phospholipase C (PLC), leading to a redistribution of intracellular Ca^{2+} that promotes insulin exocytosis. Glucokinase (GK) activators increase glucose flux into glycolysis and imeglimin acts on mitochondria. DAG, diacylglycerol; GLUT, glucose transporter isoform; GPR, G protein–coupled receptor; IP3, inositol trisphosphate; Kir, inwardly rectifying potassium channel; PKA, protein kinase A; PKC, protein kinase C; SUR, sulfonylurea receptor.

Randomized controlled studies in type 2 diabetes have shown improved glycaemic indices with imeglimin as monotherapy and an add-on to metformin or a DPP-4 inhibitor [23].

Incretins

GLP-1 receptor agonists (exenatide, liraglutide, lixisenatide, dulaglutide, and semaglutide) potentiate insulin secretion and suppress glucagon secretion when glucose concentrations are raised, delay gastric emptying, and exert a satiety effect (Figure 79.3). In addition to their glucose-lowering and weight-reducing effects, these agents have either no detrimental effects or significant beneficial effects in reducing major adverse cardiovascular events and improving kidney outcomes in randomized trials in type 2 diabetes. All current GLP-1 receptor agonists are available as daily or weekly subcutaneous injections and semaglutide is also available as an oral formulation. To enable absorption across the gastric epithelium, semaglutide is combined with an absorption enhancer, sodium hydroxybenzoylamino-caprylate (SNAC), which protects the peptide from proteolytic degradation by raising the pH around the peptide and assists in transcellular absorption [24]. Although bioavailability of the oral formulation is considerably less than the injected formulation, this is compensated for by increased dosage to achieve similar efficacy in regulating blood glucose and body weight [25]. Other approaches being considered for oral delivery of GLP-1 receptor agonists include various types of nanocapsules and cell-penetration technologies, but these have yet to match the bioavailability achieved with the SNAC system [26].

A subcutaneously implanted miniature (matchstick-sized) osmotic pump (ITCA-650) that delivers exenatide continuously for up to 48 weeks has shown comparable efficacy to once-weekly injections and awaits approval by regulatory authorities. Pre-clinical studies have provided proof of principle for other approaches to continuous GLP-1 delivery, including transdermal patches and various depot formulations. An example of the latter is the subcutaneous injection of a DPP-4-resistant GLP-1 analogue linked with the soluble fusion protein elastin-like-polypeptide (ELP). ELP forms a gel at body temperature and serves as a reservoir for the GLP-1 analogue, which can be released by local proteases [27].

Although the molecular structures of GLP-1 receptor agonists are modified from native GLP-1 to prevent rapid breakdown by DPP-4, the incidence of anti-drug antibody production appears to be low and there is little evidence of a significant loss of drug efficacy. Nevertheless, small-molecule (non-peptide) GLP-1 receptor agonists should enable oral delivery and avoid antibody interference, and several such molecules have recently shown sufficient potency to progress into clinical trials [28]. In addition to GLP-1, several further gastrointestinal and pancreatic hormones, analogues, or small-molecule receptor agonists or antagonists have

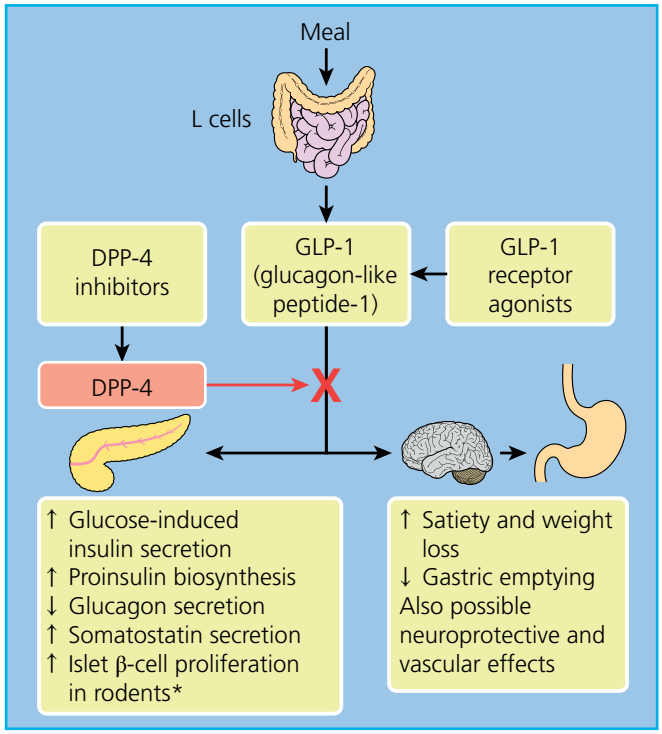

Figure 79.3 Actions of glucagon-like peptide 1 (GLP-1). GLP-1 is a key incretin hormone that enhances the insulin response to enteral glucose. Intestinal glucose stimulates secretion of GLP-1 by L cells. The effects of GLP-1 on glucose homeostasis include pancreatic effects (potentiation of insulin release and reduced glucagon release, each in a glucose-dependent manner), increased satiety, and delayed gastric emptying. GLP-1 is rapidly inactivated by the enzyme dipeptidyl peptidase 4 (DPP-4). DPP-4 inhibitors prolong the activity of endogenous GLP-1. GLP-1 receptor agonists are analogues that are altered from native GLP-1 to protect against degradation by DPP-4. *Effect seen in pre-clinical studies but not confirmed in human type 2 diabetes.

been considered as possible therapies for use in the management of type 2 diabetes. Their actions are summarized in Table 79.3 and several are considered in what follows.

Peptide mixtures

Advances in formulation chemistry have enabled the preparation of mixtures of peptides with different physico-chemical properties to achieve sufficient stability for storage together and administration in a single injection. Simultaneous delivery of two or more peptides with complementary actions offers the opportunity to conveniently expand the range of therapeutic effects and gain additive efficacy while using lower doses of the individual components, thereby reducing side effects. The complementary actions of GLP-1 receptor agonists (mainly targeting post-prandial hyperglycaemia) and basal insulin (mainly targeting basal hyperglycaemia) are now combined in mixtures of the two peptides (*fixed-ratio* combinations) that have been formulated into a single subcutaneous injection. For example, IDegLira contains liraglutide with insulin degludec (3.6 mg: 100 units) and LixiLan contains lixisenatide with glargine (50 µg: 100 units) [29]. The combinations are titrated as for basal insulin, and randomized studies in type 2 diabetes have noted that the combinations can give greater reductions in HbA_{1c} than with either agent alone, while requiring less insulin, avoiding weight gain, and incurring a reduced risk of hypoglycaemia.

Several combinations of gastrointestinal and pancreatic hormones have been tested by co-administration separately and/or in mixtures [30]. For example, in pre-clinical and clinical studies, co-administration of GLP-1 with glucagon reduced hyperglycaemia and increased energy expenditure, while co-administration of GLP-1 with GIP reduced hyperglycaemia and body weight, in each case to a much greater extent than with an individual agent alone. Similarly, hyperglycaemia, food intake, and body weight were decreased with triple co-administration of GLP-1, glucagon, and GIP as well as with triple co-administration of GLP-1, oxynto-

Table 79.3 Glucoregulatory effects of gastrointestinal and pancreatic peptides in clinical use or being investigated as templates to develop therapeutic interventions for type 2 diabetes.

	Source	HbA_{1c}	Body weight	Food intake	Energy expended	Insulin β-cell mass	Glucagon secretion
GIP	K cells	↓	?*^	?*^	↓	↑	↑
GLP-1	L cells	↓	↓	↓	?	↑	↓
Glucagon	A cells	↑	↓	↓	↑	↑	↔
Insulin	B cells	↓	↑	↓	↓↔↑*	↔	↓
Pramlintide$	(β cells$)	↓	↓	↓	?	?	↓
Peptide YY	L cells	↔	↓	↓	?	?	↔↓
Oxyntomodulin	L cells	↓	↓	↓	↑	↑	?
Gastrin	G cells	↔	↔	↓	↔	↑	?
CCK	I cells	↔	↔	↓	↔	↔	↔
Xenin	K cells	↔	↓	↓	?	↑	?
Ghrelin	Gr(X/A) cells	↑?	↑	↑	?	↓*	↑
Obestatin	Gr(X/A) cells	↔	?	↓	?	?	?

↑, increase; ↓, decrease; ↔, no clear change; ?, uncertain; *, depends on pathophysiological circumstances; ^, may vary between species; $, pramlintide is an analogue of islet amyloid polypeptide produced by pancreatic β cells.
CCK, cholecystokinin; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1; HbA_{1c}, glycated haemoglobin; peptide YY, peptide tyrosine tyrosine.

modulin, and peptide YY [30–33]. In pre-clinical studies co-administration of GLP-1 with either gastrin or cholecystokinin-8 (CCK-8) has increased islet β-cell mass and assisted appetite control, while extra glucose-lowering efficacy has been noted when xenin is co-administered with GLP-1 or GIP. Although the amylin analogue pramlintide has long received minority use in insulin-treated individuals in some regions to reduce appetite and weight gain, pre-clinical studies have shown that co-administration of pramlintide with GLP-1 can accentuate appetite regulation and increase weight loss. Similarly, combination of another amylin analogue (cagrilintide) with a GLP-1 receptor agonist has been reported to produce large reductions body weight together with improved glycaemic levels. Because many of these peptides are not readily mixed together at the concentrations required for a single injection, attention has been given to the development of hybrid peptides that are designed to interact with a specified selection of receptors to create a desired therapeutic profile (single-molecule multi-agonists).

Hybrid peptides

Single-peptide molecules that can interact with several different receptors can be produced by fusion of different molecules or by selection of amino acid sequences that interact with particular receptors, and linking these sequences together to produce a unique chimeric molecule. The latter approach has given rise to clinical studies with several dual receptor agonists (e.g. GLP-1/GIP, GLP-1/glucagon) and triple receptor agonists (e.g. GLP-1/GIP/glucagon) (Figure 79.4). Many of the subtleties in the design of these molecules are concerned with achieving an appropriate balance of effects at the different target receptors while retaining peptide stability and reducing the risk of anti-drug antibody production.

Several dual GLP-1/GIP receptor agonists have been studied in people with type 2 diabetes, the most advanced in development being tirzepatide (LY3298176) [34, 35]. This is a 39 amino acid peptide based on the biologically active N-terminal GIP(1–14) sequence with an N2 aminoisobutyric acid substitution to prevent degradation by DPP-4 (Figure 79.4). The mid-sequence confers GLP-1 receptor agonism, and a C20 fatty di-acid chain linked via glutamic acid to Lys20 facilitates attachment to albumin to prolong viability in the circulation. The molecule is a stronger agonist at the GIP receptor than the GLP-1 receptor to account for the physiologically higher circulating concentrations of GIP than GLP-1.

A 26-week phase 2 double-blind placebo-controlled study of 316 individuals with type 2 diabetes treated by lifestyle plus metformin (baseline HbA_{1c} 8.2% [66 mmol/mol], body weight 92 kg, and body mass index [BMI] 32 kg/m^2) compared once-weekly subcutaneous injection of tirzepatide (1, 5, 10, and 15 mg), dulaglutide (1.5 mg), and placebo [35]. The tirzepatide was associated with dose-related reductions in HbA_{1c} by 1.00%, 1.67%, 1.83%, and 1.89% (~11–20 mmol/mol) for the 1, 5, 10, and 15 mg doses, respectively, compared to placebo. In comparison, dulaglutide reduced HbA_{1c} by 1.21% (13 mmol/mol), suggesting that high doses of tirzepatide exceeded the glucose-lowering efficacy of the highest dose of dulaglutide in current clinical use. Tirzepatide also markedly reduced body weight in a dose-dependent manner (by 0.9 kg at the 1 mg dose to 11.3 kg at the 15 mg dose), compared with reductions of 2.7 kg for dulaglutide and 0.4 kg for placebo. The tirzepatide also slightly lowered circulating triglyceride concentrations and blood pressure and did not cause hypoglycaemia. However, the higher doses of tirzepatide were associated with a high incidence of initial gastrointestinal disturbances and with the development of anti-drug antibodies, although these were generally of low titre and did not appear to compromise efficacy.

GLP-1/glucagon receptor co-agonists studied in individuals with type 2 diabetes have been based mostly on oxyntomodulin, which itself exerts relatively weak agonist effects at both GLP-1 receptors and glucagon receptors, but is amenable to minor

GLP-1, GIP, glucagon and oxyntomodulin

GLP-1	**HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRG**
GIP	**YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQ**
Glucagon	**HSQGTFTSDYSKYLDSRRAQDFVQWLMNT**
Oxyntomodulin	**HSQGTFTSDYSKYLDSRRAQDFVQWLMNTKRNRNNIA**

GLP-1/GIP dual agonists

Twincretin[a]	**YXEGTFTSNYSIYLNKQAAXEFVNWLLAGGPSSGAPPPSK**
Hybrid[b]	**YAEGTFISDYSIAMDYSSYLEGQAAKEFIAWLVKGKKNDWKHNITQGPSSGAPPPS**
Tirzepatide[c]	**YXEGTFTSDYSIXLDKIAQKAFVQWLIAGPSSGAPPPS-NH_2**

GLP-1/glucagon dual agonist

Cotadutide[d]	**HSQGTFTSDKSEYLDSERARDFVAWLEAGG**

GLP-1/GIP/glucagon triple agonists

Triagonist A[e]	**HXQGTFTSDKSKYLDERAAQDFVQWLLDGGPSSGAPPPS-NH_2**
Triagonist B[f]	**YAEGTFISDYSKYLDSRRAQDFIAWLVKGR-NH_2**
XFL6[g]	**EGTFQAKQWLPQDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS**

Figure 79.4 Examples of dual and triple co-agonist hybrid peptides. These receptor co-agonists have used glucagon-like peptide 1 (GLP-1), glucagon, glucose-dependent insulinotropic polypeptide (GIP), or oxyntomodulin as their foundation structure, and the structure has then been modified to confer agonism at other peptide receptors. Amino acid residues are indicated by the letter code. The presence of an alanine (A) or serine (S) amino acid residue at the N-terminal position 2 renders these molecules vulnerable to degradation by DPP-4, hence the engineered co-agonists are usually modified in this position. A, *D*-Ala (dextrorotary alanine); X, aminoisobutyric acid. Superscript letters denote original descriptions of peptide sequences: [a]Finan et al. 2013 [83]; [b]Pathak et al. 2018 [84]; [c]Coskun et al. 2018 [34]; [d]Ambery et al. 2018 [36]; [e]Finan et al. 2015 [32]; [f]Gault et al. 2013 [37]; [g]Cui et al. 2020 [85].

sequence adjustments to modify efficacy. This co-agonist combination captures the appetite-suppressing, insulin-releasing, and energy-expending effects of each agent to promote weight loss, while the GLP-1 agonist moiety can suppress endogenous glucagon secretion and the insulin-releasing effects can overcome the hyperglycaemic effect of the glucagon moiety to achieve overall glucose lowering. Cotadutide (MEDI0382), for example, is an oxyntomodulin-based GLP-1/glucagon receptor co-agonist studied in a 49-day phase 2 randomized placebo-controlled trial with 65 overweight and obese individuals with type 2 diabetes [36]. Daily subcutaneous injections of cotadutide (50 μg escalated to 300 μg) produced clinically significant reductions in body weight (~3 kg), HbA_{1c} (~0.7%; 8 mmol/mol), and basal and post-prandial glycaemia, and increased meal-stimulated insulin.

Pre-clinical studies in obese and diabetic rodents have assessed various GLP-1/GIP/glucagon receptor tri-agonists and noted improved glucose tolerance, increased insulin secretion, and reduced body weight [31, 32, 37, 38]. Pre-clinical studies of other combinations of triple receptor agonists such as an exendin-4/gastrin/xenin-8 tri-agonist have shown similar efficacy [39]. In addition to the potential benefits of multireceptor agonists for the treatment of type 2 diabetes and obesity, there is emerging evidence that incretin-based multireceptor agonists could assist in the management of hyperlipidaemias, hepatic steatosis, degenerative bone diseases, neurological disorders, and cardio-renal conditions [40]. It is also noted that incretin peptides have been attached to steroid molecules (e.g. oestrogens and glucocorticoids) and thyroid hormones, indicating opportunities to target other therapies [31, 41].

Dipeptidyl peptidase 4 inhibitors and bile acid receptor agonists

Inhibitors of the enzyme DPP-4 (EC 3.4.14.5) are widely used in the treatment of type 2 diabetes to prevent the breakdown of endogenous incretins, particularly raising endogenous GLP-1 concentrations [42]. They include sitagliptin, saxagliptin, linagliptin, and alogliptin taken once daily, and vildagliptin taken twice daily. Other DPP-4 inhibitors are available in some regions including once-weekly agents such as omarigliptin and trelagliptin, and further DPP-4 inhibitors are reported to be in development, offering similar properties to those already available.

Another approach to raise endogenous GLP-1 could involve TGR5 (GP-BAR1) bile acid receptors, which are strongly expressed by intestinal L cells, and activation by bile acids enhances GLP-1 secretion [43]. The bile acid sequestrant colesevelam, which has an indication for the treatment of hyperglycaemia in individuals with type 2 diabetes in some regions, carries bile acids more distally along the intestinal tract and has been associated with a small rise in GLP-1. However, TGR5 receptors are mostly located in the basolateral membranes of L cells, suggesting that activation by agents in the intestinal lumen may require large doses.

Modifiers of glucagon secretion and action

The therapeutic potential for stimulants and inhibitors of glucagon secretion and action continues to be debated. As already noted, the appetite-suppressing, energy-expending, weight-lowering, and insulin-releasing effects of glucagon are used to advantage in glucagon-based and oxyntomodulin-based hybrid peptides, provided that concomitant intervention over-rides the hyperglycaemic effect of hepatic glucose output induced by glucagon receptor activation. The hyperglycaemic effect of glucagon is part of the normal physiological response to protect against hypoglycaemia, and glucagon administration is used to reverse insulin-induced hypoglycaemia in type 1 diabetes. However, administration of glucagon to treat hypoglycaemia is not encouraged in type 2 diabetes due to the strong insulin-releasing effect of glucagon.

Glucagon concentrations are typically inappropriately raised in type 2 diabetes, and blood glucose can be lowered by suppression of glucagon secretion from pancreatic α cells (e.g. with GLP-1 receptor agonists, somatostatin analogues, or non-peptide inhibitors), or by suppression of glucagon action using peptide glucagon receptor antagonists, anti-glucagon antibodies, or glucagon receptor antisense oligonucleotides. A catalogue of small-molecule glucagon receptor antagonists has been examined, but glucagon receptor antagonism is associated with compensatory hyperglucagonaemia, such that rebound hyperglycaemia occurs if continuous therapy is interrupted. Also, unwanted liver effects have further complicated the therapeutic application of glucagon receptor antagonism [44].

Insulin mimetic agents

Insulin resistance is a prominent feature of most forms of type 2 diabetes, typically reflecting the cumulative detrimental impact of multiple pathogenic factors that disrupt the kinase activity of insulin receptors and signalling intermediates along the post-receptor pathways. The resulting diversity of presentations of insulin resistance has complicated the search for agents to override or circumvent the *pinch points* [45]. Normal binding of insulin molecules to extracellular regions of the insulin receptor at spatially separated sites on the α subunits is difficult to replicate using small molecules [46, 47]. However, conformational changes similar to those produced by insulin binding may be achieved in other ways, as indicated by a monoclonal antibody that interacts with the insulin receptor at different sites to insulin, but creates a conformational adjustment to the receptor that initiates some of the metabolic effects of insulin, sufficiently to improve glucose homeostasis in insulin-resistant diabetic animals [48]. There is also proof of principle that conformational changes to the insulin receptor induced by small molecules can elicit some metabolic effects of insulin. This has been shown with several compounds, such as the fungal metabolite chaetochromin that interacts with the extracellular portion of the insulin receptor to initiate some actions of insulin independently of insulin binding to the receptor [49]. Small molecules might also be able to bypass the extracellular domains of the insulin receptor and interact with cytosolic regions of the β subunits of the receptor to activate receptor signalling without insulin binding, as shown for example with another fungal metabolite, demethylasterriquinone [50]. However, although several small molecules have been reported to activate the insulin receptor, these have yet to gain clinical validation [51].

Insulin action potentiators

Many compounds will potentiate insulin action after insulin has initiated a conformational change to the receptor and enabled tyrosine phosphorylation of the β subunits. For example, insulin action is enhanced and prolonged by agents that prevent receptor

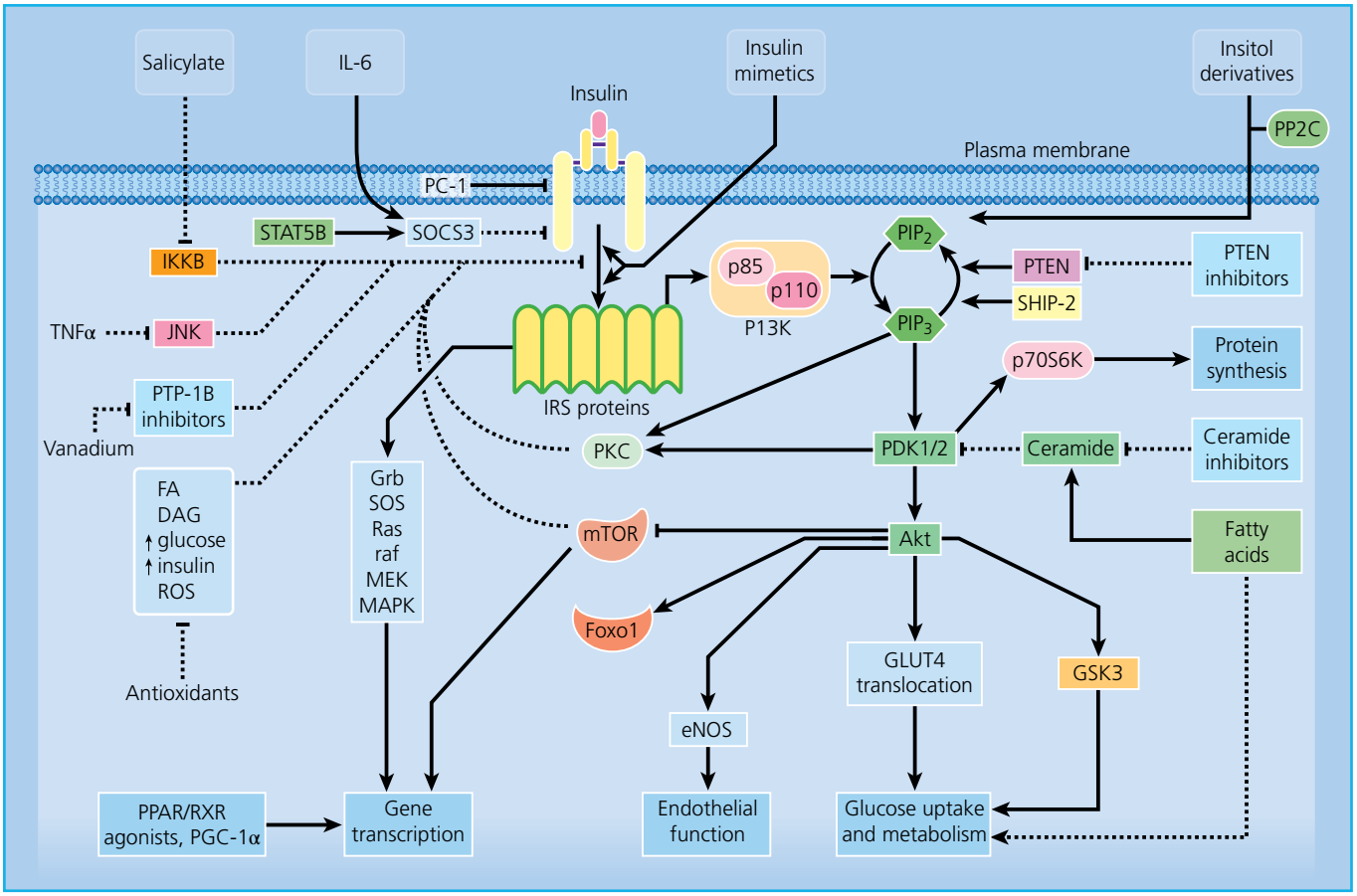

Figure 79.5 Pathways of intracellular insulin signalling illustrating potential sites for therapeutic intervention. Insulin binds to the α subunits of the extracellular region of the insulin receptor, producing conformational changes that extend into the intracellular regions and alter the conformation of the β subunits of the receptor. This allows the β subunits to be phosphorylated on tyrosine residues, which enables the β subunits to act as tyrosine kinase enzymes to phosphorylate a collection of insulin receptor substrate (IRS) proteins. The phosphorylated IRS proteins initiate signalling along the intracellular pathways that control the diverse biological effects of insulin. Many of the signalling steps are restricted (*pinch-points*) by factors contributing to insulin resistance, and these steps are potential targets for therapeutic interventions. AKT, protein kinase B (PKB); AMPK, adenosine monophosphate-activated protein kinase; DAG, diacylglycerol; eNOS, endothelial nitric oxide synthase; FOXO1, forkhead box protein O1A; GLUT, glucose transporter isoform; Grb, growth factor receptor binding protein; GSK3, glycogen synthase kinase 3; IKKB, inhibitor κB kinase-β; IL-6, interleukin 6; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PC-1/NNP1, glycoprotein 1; PDK, phosphoinositide-dependent protein kinase; PGC-1α, PPAR co-activator 1α; PI3K, phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol-3,4-bisphosphate; PIP3, phosphatidylinositol-3,4,5-trisphosphate; PKC, protein kinase C; PPAR, peroxisome proliferator-activated receptor; PP2C, pyruvate dehydrogenase phosphatase (protein phosphatase 2C); PTEN, phosphatase and tensin homologue; PTP-1B, protein tyrosine phosphatase 1B; Raf, a serine–threonine protein kinase; Ras, a guanosine triphosphatase; ROS, reactive oxygen species; RXR, retinoid X receptor; SHIP-2, src homology-2-inositol phosphatase; SOCS-3, suppressor of cytokine signalling-3; SOS, sons of sevenless; STAT, signal transducer and activator of transcription; TNF-α, tumour necrosis factor α; ↑, increase.

dephosphorylation by suppressing phosphatase enzyme activity. Included here are inhibitors of protein tyrosine phosphatase 1B (PTP1B) and less specific phosphatase inhibitors, notably vanadium compounds (Figure 79.5). Although some of these compounds have shown efficacy during initial clinical studies, off-target effects and/or a narrow therapeutic window have so far precluded further development [52, 53].

Another approach to extend the signalling time of activated insulin receptors and insulin receptor substrate (IRS) proteins has been to interrupt the negative feedback effects of more distal intermediates within the insulin action pathways. Certain isoforms of PKC mediate the negative effects of excess fatty acids, diacylglycerol, and products of glucotoxicity, in part by phosphorylation of the receptor and IRS proteins at serine or threonine sites [54]. Although some PKC inhibitors have increased insulin action and shown promise in the treatment of diabetic retinopathy and neuropathy, this approach has yet to prove sufficiently effective for the management of hyperglycaemia in type 2 diabetes. Other signalling intermediates that inhibit the activity of insulin receptors or IRS proteins by serine phosphorylation have also been considered as potential therapeutic targets. These include inhibitor κB kinase-β (IKKβ) and c-Jun N-terminal kinase (JNK), which mediate the insulin resistance produced by certain cytokines such as tumour necrosis factor α (TNF-α) and the mammalian target of rapamycin (mTOR), which mediates a negative feedback from AKT (protein kinase B) [45]. Supplementing the availability of substrates for post-receptor steps is a further intervention to enhance insulin action, as illustrated by the administration of methylchiroinositol (pinitol), which facilitates signalling through phosphatidylinositol 3-kinase and has improved glycaemic indices in animal models of insulin resistance and insulin deficiency [45].

Adipokines

Several peptides and other substances produced by adipose tissue can affect the endocrine pancreas, insulin action, food intake, and/or energy expenditure, and some have been explored as potential therapeutic leads [55] (Figure 79.6). For example, leptin exerts centrally mediated satiety and thermogenic effects, acts directly on tissues to improve insulin action and suppress glucagon, and facilitates weight loss. However, therapeutic doses of leptin and leptin analogues generate leptin resistance, which severely compromises long-term efficacy, although a leptin analogue is used in some regions to treat lipodystrophy and congenital leptin deficiency [56].

Adiponectin offers a range of potentially advantageous effects, including increased insulin sensitivity, improved endothelial function, and reduced inflammation, but the amounts of adiponectin released by adipose tissue are reduced in people with overweight or obesity with type 2 diabetes. Supplementary adiponectin itself may not be a realistic intervention, but small-molecule agonists of the adiponectin receptors could provide a suitable alternative, and initial pre-clinical studies have indicated that this approach can reduce insulin resistance and improve glycaemic management [57]. Several other adipocyte hormones have been implicated in the pathogenesis of type 2 diabetes, but their therapeutic potential remains to be determined [55]. For example, resistin and retinol-binding protein 4 reduce insulin sensitivity, whereas omentin and visfatin appear to improve insulin sensitivity. Many of the adipocyte peptides influence inflammatory processes, and the major proinflammatory adipokines, TNF-α, and interleukin 6 (IL-6) have been implicated in insulin resistance, but it is unclear whether these are appropriate targets for glucose-lowering purposes [58].

Fibroblast growth factor 21 (FGF21) is secreted by adipose tissue, liver, and muscle, and in pre-clinical studies has improved insulin sensitivity and β-cell survival, in addition to promoting fatty acid oxidation and hepatic gluconeogenesis during fasting. However, type 2 diabetes in individuals with obesity appears to be associated with resistance to FGF21, and plasma concentrations of FGF21 are often raised. Nevertheless, clinical studies with FGF21 analogues have shown improvements in insulin sensitivity, glycaemic indices, and the blood lipid profile, possibly due in part to increased production of adiponectin [59, 60].

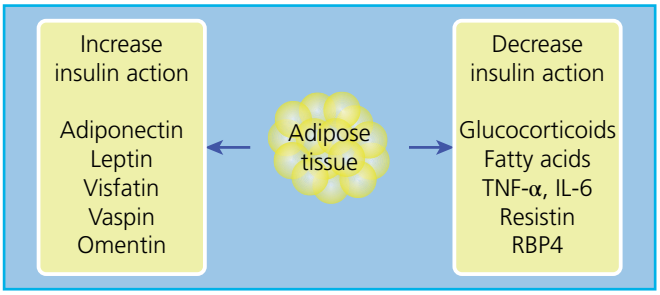

Figure 79.6 Proteins secreted from adipose tissue that can increase or decrease insulin action. These proteins or their receptors are potential targets or templates for therapeutic agents to improve glycaemic control. IL-6, interleukin 6; RBP4, retinol-binding protein 4; TNF-α, tumour necrosis factor α.

Peroxisome proliferator-activated receptor γ agonists

The insulin-sensitizing effects of thiazolidinediones (e.g. pioglitazone) are mostly mediated by activation of the nuclear transcription factor peroxisome proliferator-activated receptor γ (PPARγ). Redesigned PPARγ agonists have not been able to eliminate unwanted side effects such as fluid retention, increased adiposity, and bone resorption, which have limited suitability for routine clinical use. Dual agonists of PPARγ and PPARα (known as glitazars) incorporate the advantage of the lipid-lowering and anti-inflammatory effects of PPARα, but also have encountered problematic side effects [61, 62]. Triple PPARγ/α/δ agonists (pan-PPARs) have the additional properties of increased energy expenditure and weight loss conferred by PPARδ agonism, but these agents have yet to receive clinical sanction (Figure 79.7). Nevertheless, selective manipulation of PPAR-mediated activities continues to be explored, and PPAR agonist molecules are being considered for the treatment of hepatic steatosis.

Hydroxysteroid dehydrogenase 1 inhibitors

Raised glucocorticoid concentrations can precipitate and aggravate truncal obesity, insulin resistance, and hyperglycaemia, whereas interventions to reduce glucocorticoid action can prevent and reverse these effects. The enzyme 11β-hydroxysteroid dehydrogenase 1 (11βHSD1) converts cortisone to active cortisol mostly within liver and adipose tissue and without substantially affecting circulating cortisol. Inhibitors of 11βHSD1 have reduced cortisol production within these tissues, associated with improvements in insulin sensitivity, glycaemic indices, and the lipid profile of people with type 2 diabetes while enabling weight loss [63, 64]. However, it has proved difficult to avoid some reduction of circulating cortisol, which gives rise to a compensatory increase in adrenocorticotropic hormone (ACTH), and the outcome of long-term trials is awaited.

Sodium–glucose cotransporter inhibitors

Intestinal absorption of glucose is mediated via SGLT-1 in the brush border of enterocytes, while reabsorption of glucose that is filtered by the kidney is mediated mostly (~90%) via SGLT-2 in the initial part of the proximal tubules, and the remainder is reabsorbed via SGLT-1 in more distal parts of the proximal tubules (Figure 79.8). SGLT inhibitors in current clinical use (e.g. canagliflozin, dapagliflozin, empagliflozin, ertugliflozin) predominantly inhibit SGLT-2, lowering the renal threshold for glucose and eliminating excess glucose in the urine (glucosuria) [65]. This provides an insulin-independent mechanism to lower blood glucose and dispose of calories, thereby assisting in weight loss (Chapter 35). The osmotic diuresis that accompanies the glucosuria may contribute in part to a lowering of blood pressure, and there is considerable evidence that these agents confer cardio-renal protection by reducing the onset and progression of heart failure and slowing the age-related decline in glomerular filtration rate [66]. Additional SGLT-2 inhibitors have been developed and are available in some regions. There are also variants that exert a significant inhibitory effect against both SGLT-2 and SGLT-1, such as sotagliflozin [67]. This latter type of agent can

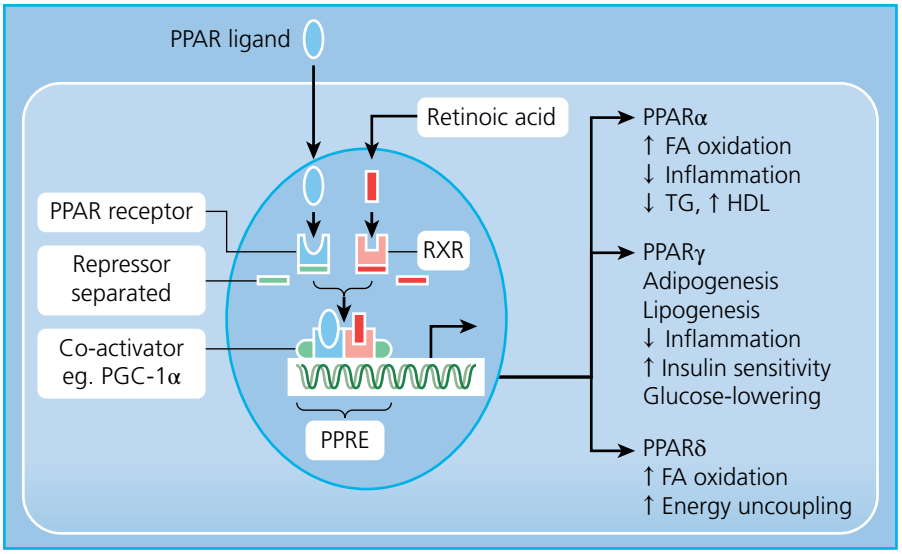

Figure 79.7 Cellular mechanism of action of a peroxisome proliferator-activated receptor (PPAR) ligand. The PPAR ligand binds to its nuclear PPAR receptor, which forms a heterodimer with the retinoid X receptor (RXR). Ligand binding releases repressors, attracts co-activators, and exposes the active site of the receptor that binds with its specific DNA nucleotide sequence – peroxisome proliferator response element (PPRE). RNA polymerase is recruited for transcription of mRNA from genes that carry the PPRE sequence in a promoter region. The mRNA is translated into the enzymes and transporters responsible for the biological effects. There are three types of PPAR agonists: PPARγ, PPARα, and PPARδ. Each type of agonist offers a range of effects. PPARγ agonists enhance lipogenesis, adipogenesis, insulin sensitivity, and glucose lowering, PPARα agonists have lipid-lowering and anti-inflammatory effects, and PPARδ agonists promote energy expenditure. Selective structural modifications to agonist molecules provide an opportunity to retain and accentuate desired effects while reducing unwanted effects. FA, fatty acids; HDL, high-density lipoprotein; PGC-1α, PPAR co-activator 1α; TG, triglyceride.

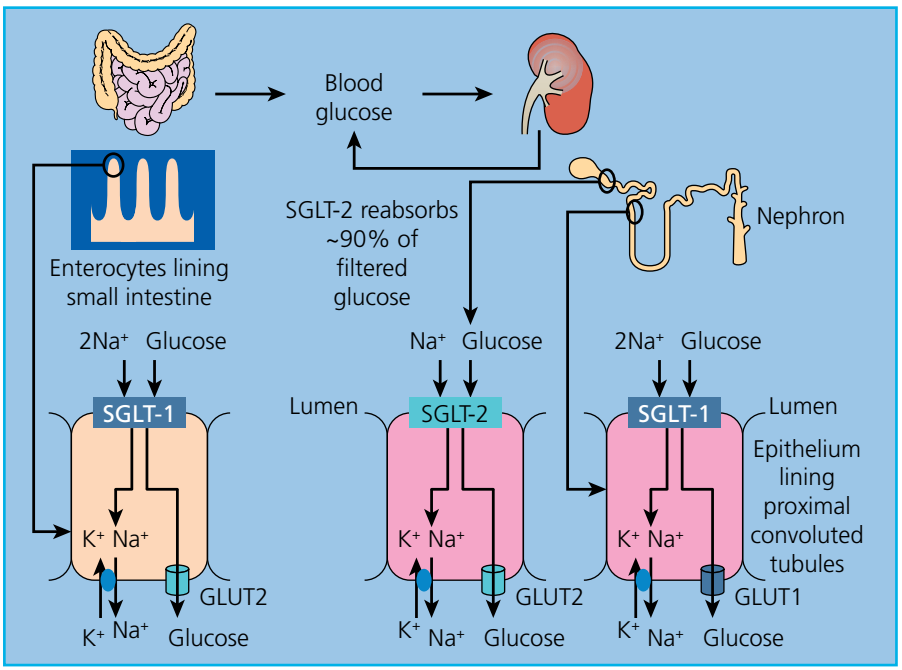

Figure 79.8 Sites of action of sodium–glucose co-transporters SGLT-1 and SGLT-2. SGLT-1 is responsible for intestinal glucose absorption and SGLT-2 is the main transporter responsible for glucose reabsorption from renal proximal convoluted tubules. SGLT-1 also contributes to glucose reabsorption from the renal proximal convoluted tubules. GLUT, glucose transporter.

defer glucose absorption more distally along the intestinal tract, slow the appearance of glucose in the portal circulation, and increase the secretion of GLP-1 from ileal L cells. However, to avoid unabsorbed glucose passing into the large bowel, these agents must be absorbed or denatured along the intestinal tract. Because the inhibition of SGLT-2 increases the passage of extra glucose along the proximal tubules, it appears to upregulate SGLT-1 that is expressed in more distal parts of the proximal tubules: thus, it is possible that an agent capable of inhibiting SGLT-1 could also increase glucosuric efficacy.

Evidence that SGLT-2 inhibition can reduce the onset and severity of heart failure with reduced or preserved ejection fraction and

preserve renal function in people without diabetes as well as with diabetes has provided a new impetus to research with this class of agents. Accordingly, established and new inhibitors of SGLT-2 are being investigated to capitalize on these properties.

Modifiers of nutrient metabolism

Suppression of hepatic gluconeogenesis and/or glycogenolysis can reduce blood glucose, but such effects must only be partial and promptly limited by counter-regulatory mechanisms to prevent significant hypoglycaemia [68]. Reduced mobilization of glycogen stores by inhibitors of glycogen phosphorylase has lowered blood glucose in pre-clinical studies, but clinical efficacy has been modest or unsustained. Glucose 6-phosphatase inhibitors prevent the last step in glucose output from both glycogenolysis and gluconeogenesis, but their activity is not easily terminated and the risk of hypoglycaemia is increased. Inhibitors of fructose 1,6-bisphosphatase prevent the dephosphorylation of fructose 1,6-bisphosphate to fructose 6-phosphate, which is the penultimate step in gluconeogenesis before glucose 6-phosphate. These inhibitors can maintain a partial reduction of hepatic glucose output due to increased compensatory glycogenolysis, and clinical studies are ongoing [69].

Many substances directly stimulate glucose uptake and utilization by muscle and adipose tissue, but few have been advanced for a therapeutic application in type 2 diabetes, as their effects are difficult to control and side effect profiles are not suitable. Examples include dichloroacetate, spermine, diamides, various peroxides, vitamin K_5, deoxyfrenolicin, okadaic acid, and several phorbol esters [15]. Inhibitors of glycogen synthase kinase have increased glycogenesis and lowered blood glucose in insulin-resistant diabetic animals, but potential adverse effects on the control of cellular division have deterred development for type 2 diabetes.

Agents that activate adenosine 5′-monophosphate-activated protein kinase (AMPK) have improved glycaemic indices in pre-clinical studies and attracted interest as therapies for type 2 diabetes. AMPK is a key energy-regulating enzyme that appears to be one of several targets for metformin, some PPARγ agonists, and adiponectin receptor agonists. It is activated when cellular energy status declines and AMP concentrations rise, promoting the uptake and oxidation of glucose and fatty acids to restore ATP production. AMPK also reduces gluconeogenesis and lipogenesis, and may have a tumour-suppressor effect [70]. Analogues of AMP, α-lipoic acid, various polyphenols, salicylates, and other small molecules have been identified as activators of AMPK, and more extensive clinical evidence is awaited to assess efficacy and off-target effects such as effects on other AMP-sensitive enzymes [70].

Tissue selective and smart insulins

The drainage of endogenous insulin from the pancreas into the portal circulation normally delivers a much higher concentration of insulin to the liver than to the periphery, but this difference in tissue exposure is not achieved by subcutaneous injection of exogenous insulin. To deliver more exogenous insulin to liver cells than muscle cells, insulin analogues have been attached to large carrier molecules such as polyethylene glycol, albumin, or thyroid-binding protein that move freely through the fenestrated hepatic sinusoids, but provide limited access through the tighter peripheral capillary endothelia [71]. Further exploration of these and other approaches to improve hepato-selectivity of insulins continue in development.

To adjust the supply of insulin in concert with the prevailing glucose concentration, proof of principle has been established for glucose-responsive *smart* insulins, which are released from a circulating chemical complex or an implanted depot by direct chemical interaction with glucose. For example, glucose will displace insulin that is inactive when linked to a boronic acid derivative, so as the glucose concentration increases, more insulin is released [72]. Also, polymers containing boronic acid derivatives can be cross-linked by glucose. If these polymers are included in hydrogels containing insulin, the cross-links formed by an increased concentration of glucose will deform the polymer and squeeze out insulin [73]. Further glucose-responsive approaches include insulin patches that incorporate glucose oxidase to register changes in the glucose concentration and release insulin accordingly.

Anti-obesity agents

Losing weight by reducing food intake or increasing energy dissipation, and the long-term reduction of adiposity, improve insulin sensitivity and improve glycaemic indices in individuals with overweight or obesity and type 2 diabetes. Indeed, very low-calorie diets and bariatric surgery have produced laudable results in this respect [74, 75]. However, there has been a reluctance to manage hyperglycaemia through pharmacological interventions primarily designed for weight loss. The intestinal lipase inhibitor orlistat is a widely used weight-reducing therapy, and several centrally acting satiety-inducing agents are available in some regions. These agents include the amphetamine-like sympathomimetic phentermine, a phentermine–topiramate combination, and a bupropion–naltrexone combination. A 5HT2c serotonin receptor agonist (lorcaserin) has been withdrawn. Each of these agents improves glycaemic indices in individuals with overweight and obesity with type 2 diabetes, but it is uncertain whether these agents exert significant glucose-lowering effects independently of reduced adiposity [76]. Although GLP-1 receptor agonists and SGLT-2 inhibitors already combine glucose-lowering and weight-reducing properties, it would be highly advantageous if future attention could strongly target the coexisting problems of obesity and diabetes.

Epigenetic and pharmacogenomic factors

Epigenetic opportunities for glucose lowering have come to attention through the effects of sirtuin enzymes. Sirtuins are nicotinamide adenine dinucleotide (NAD)–dependent histone deacetylases and adenosine diphosphate (ADP) ribosyltransferases that alter histone structure and chromatin stability. This in turn alters the transcription of genes that influence mitochondrial biogenesis and energetics. These effects plus the actions of sirtuins on non-histone proteins modulate insulin secretion and nutrient metabolism to mimic caloric restriction, and protect against weight gain, diabetes, and cardiovascular disease in animal models [77]. Several small-molecule sirtuin activators have delivered initially encouraging effects in animal models of diabetes, but inconsistencies in these studies suggest that pharmacological interventions will need to discriminate between the activation of specific sirtuins to create the desired profile of effects.

The recognition of certain gene variants can help to predict the likely efficacy, tolerability, and risk of adverse effects with a particular glucose-lowering agent (e.g. metformin, sulfonylurea, thiazolidinedione) for an individual. Gene variants for transporter proteins that affect the absorption, cellular distribution, and elimination of drugs, and also variants encoding the enzymes involved in their metabolism, influence responses to these drugs within the genetic constraints of the disease process itself [78]. However, the predictive capacity of pharmacogenomics is complicated by the vast numbers of genes that can have impacts on the pharmacokinetics and pharmacodynamics of drug therapies in type 2 diabetes, but as pharmacogenomic testing is refined it will offer valuable clinical utility to improve drug–patient compatibility and reduce the risk of ineffective or harmful interventions.

Using pharmacogenomics to design new drug therapies presents a particular challenge for the treatment of type 2 diabetes owing to the multivariable genetic components that contribute to the aetiology, pathogenesis, and progressive natural history of the disease [78, 79]. There is seldom a single rate-limiting protein that can be pharmacologically manipulated to reset normal glucose homeostasis, but continued mapping of genetic variants and disturbances to the diabetes proteome should identify prime contenders for future pharmacological interventions, especially to address the defects of β-cell function and survival as type 2 diabetes advances [80].

Safety

The long-term use of diabetes medications requires particular attention to long-term safety, and regulatory processes for the approval and subsequent pharmacovigilance for new glucose-lowering agents take thorough account of this requirement [81]. As noted at the start of this chapter, individuals with type 2 diabetes are prone to develop comorbidities that contraindicate some medicines, lead to drug interactions, or introduce other safety concerns. Some safety issues can take many years to emerge and necessitate revision to the label in accordance with the change in risk–benefit balance. If new medicines are to become available in a timely manner, such revisions will need to be accepted without prejudice as part of the lifespan of a medicine [82].

Conclusion

This chapter has considered glucose-lowering medications in development and potential novel therapeutic targets for type 2 diabetes. Therapeutic developments directed against type 1 diabetes are reviewed in Chapters 76 and 77. It is noted that type 2 diabetes involves such a variable mix of defects that effective management usually needs to exploit a selection of differently acting agents that can be used in combination as the disease progresses. For the future, attention to adiposity, hunger–satiety discord, energy expenditure, and inflammation may acquire greater precedence alongside more conventional approaches directed towards the secretion and actions of insulin, glucagon, and incretins. There will also be the expectation that new agents can benefit cardio-renal disturbances in diabetes as well as provide long-term metabolic management. Futuristic mechanisms might incorporate very different forms of intervention such as antisense oligonucleotides and short-interference RNA to modify the proteome, or prebiotics and probiotics to modify the microbiome. Cell-based therapies, especially glucose-sensing surrogate endocrine cells, could deliver more than insulin, and so-called smart drugs that are activated in accordance with the prevailing glucose concentration could more closely align pharmacotherapy with physiological control and obviate problems of dose titration and hypoglycaemia.

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Index

Notes: Page numbers for figures are in *italics*, tables are in **bold.**
Conditions prefixed by the word "diabetic," e.g. diabetic autonomic neuropathy, diabetic retinopathy, are indexed under the name of the condition, i.e. autonomic neuropathy, retinopathy.

AACE *see* American Association of Clinical Endocrinologists
AADE7 Self-Care Behaviours framework 356
AAV *see* adeno-associated vectors
abatacept 1129–1130
ABCC8 283–286
abdominal aortic aneurysm 755, 762–765
abdominal pain 605, 796, 801–804
ABI *see* ankle-brachial index
abscesses 890–891
absolute insulin excess 579–582, 588, 593–596
acanthosis nigricans 275–276, 282, 288–290, 838–840
acarbose 68, 70, 493, 496, 514–516
ACAS *see* Asymptomatic Carotid Atherosclerosis Study
accelerated atherosclerosis 681, 685–691, 748
accelerated fetal growth 1039–1040
access to care, universality 1109, 1114, 1116, **1118**
ACCORD trial
  cardiovascular disease 717–718, 725, 729, 735–737, 1076, 1079
  glycaemic management 348
  hyperglycaemia 682
  hypertension 695, 709
  hypoglycaemia 590
  nephropathy 647
  neuropathy 656, 664
  oral glucose lowering agents 494–495
ACE 2 *see* angiotensin-converting enzyme
ACE *see* American College of Endocrinology; angiotensin-converting enzyme inhibitors
acetylcholine 93
acetyl-coenzyme A content 238, 245
achrochordons 840
acidosis 1003
acquired immunodeficiency syndrome (AIDS) 878, 882–883, 887, 1108–1110, 1113–1117
ACST *see* Asymptomatic Carotid Surgery Trial
ACT *see* adoptive cell transfer
acupuncture 667–668
acute coronary syndromes 330, 334–335
acute graft pancreatitis 487
acute illness, hyperglycaemia 560
acute lower-limb ischaemia 760–761
acute metabolic complications 603–610
acute myocardial infarction 330, 334
acute painful neuropathy 658
acute pancreatitis 319–320
acute stroke 335, 750–752
ADA *see* American Diabetes Association
Addison disease 317, 1016
ADDQoL tool 913
adeno-associated vectors (AAV) 1145–1150
adenocarcinomas 326
adenomas 304–316
adenosine 5'-monophosphate-activated protein kinase (AMPK) 1164
adenosine triphosphate (ATP) 90–92, 225–226, 242–244
adenoviral vectors (AdV) 1145–1150
adipocytes 116, 145–146, 290–291, 506–508, 1149–1150
adipokines 89, 95–96, 1154, 1162–1164
adiponectin receptor agonists 1154, 1162–1164
adipose tissue
  body weight 144–145, 197–199, 250–254
  brown 105–107, 117, 123–124, 134–135, 1149–1150
  gene therapy 1144, 1149–1150
  glucose metabolism *78*, 80
  insulin action 123–124
  insulin resistance 238, 244–247
  insulin secretion/islet function 84, 94–96
  white 117–119, 122–123, 1149–1150
adiposity 56–57, 61, 64
adjunctive therapies 513, 816, 1026
adjustable gastric banding 554, 556
admission, in-hospital treatments 571–573, 575
adolescents
  behavioural factors 907, 910–919, 1022–1030
  blood glucose 1019–1027
  body weight 1027–1029
  burnout 1019–1020, 1026, 1029
  chronic complications 1027–1028
  continuous glucose monitoring 1019–1021, 1026–1027
  contraceptives 1027
  demography 1020
  development stages 1020–1025
  diabetic ketoacidosis 1027–1028
  education 1019–1031
  empowerment 1019, 1021–1022
  epidemiology 1020
  family factors 1019–1031
  glycaemic levels 1020–1029
  glycated haemoglobin 1020–1031
  hyperglycaemia 1020–1025, 1028–1029
  hypoglycaemia 579–580, 590, 594–597, 1020–1029
  insulin delivery 1019–1020, 1026, 1029–1031
  insulin resistance 1020–1022
  insulin therapy 1026, 1029–1031
  leaving home factors 1019–1021, 1025
  mental health 1022, 1026–1028
  multidisciplinary teams 1102–1103
  nutrition 1019–1020, 1024

Textbook of Diabetes, Sixth Edition. Edited by Richard I.G. Holt and Allan Flyvbjerg.
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adolescents (*cont'd*)
physical changes 1019–1031
pregnancy 1027
psychosocial aspects 907, 910–919, 1019–1031
self-efficacy 1019–1023, 1026–1031
self-management 1019–1031
social aspects 1019–1031
technology 1023–1026
training aspects 1019–1031
transition to adulthood 1019–1033
Type 1 diabetes 1019–1031
Type 2 diabetes 1019–1020, 1023–1029
adoptive cell transfer (ACT) therapies 487–488
ADRA2A (adrenergic receptor α2) loci 193
adrenalectomy 311
adrenaline 579–588
adrenal medulla 304, 312–314
β-adrenoceptor antagonists 299
α1-adrenoceptor antagonists 708
ADRR *see* average daily risk range
AdV *see* adenoviral vectors
Advance Care Directive/Plan 1085–1087, 1091
advanced bolus options 459, 464
advanced glycation end-products (AGE) 619–620, 681–691, 696, 814–815
ADVANCE trial 348, 495, 510, 647, 649, 682, 690, 695, 709–710, 725, 964, 1076
Afrezza 437
Africa
global burden of diabetes 29–30
Type 1 diabetes 42–45, 51
Type 2 diabetes 29–30, 55–62, 64–65, **68–69**
African Americans 978–980
AGE *see* advanced glycation end-products
ageing, skin conditions 838, 841
AGE receptor (RAGE) 681–689
age-related incidence
hypoglycaemia 579–580, 590, 594–597
infections 879
insulin resistance 241–242
NAFLD 820, 823–826, 831
obesity 250
psychotic disorders *948*
Type 1 diabetes 41–52, 204
Type 2 diabetes **29**, 55–69, 241–242
agouti-related proteins (AGRP) 131–132
AGP *see* ambulatory glucose profiles
AGRP *see* agouti-related proteins
AIDS *see* acquired immunodeficiency syndrome
AIM-HIGH trial 718
aircraft pilot licenses 960–961
air hunger 333
AKT cascade 115–116
alagebrium 686
albiglutides 526–529
Albright hereditary osteodystrophy 198
albumin 408, 640–645, 648–649
albuminuria 640–652
alcohol
dietary factors 375–376
glycaemic levels 963–964
hypoglycaemia 579–580, 588, 592–596, 963–964
recommended intake 965
risk factors 963–965
sexual dysfunction 790
travel 969
alcoholic chronic pancreatitis *296*, 324
aldose reductase inhibitors 619–620, 664–665
aldosterone hormones 304, 316
alefacept 1129
Algeria 44–45, 1108
aliskiren 649, 708
Allen, Frederick Madison 8–9, 431–432
ALLHAT study 298
alogliptin 492, 496, 509–510
alpha 2 delta ligands 666
alpha-lipoic acid 664
alprostadil 780, 787
Alstrom syndrome 198
Alzheimer's dementia 924–926, 931, 1079
Amadori 405, 619, 682
ambulatory blood pressure 700–711
ambulatory care 1004–1006
ambulatory glucose profiles (AGP) 452–457
amelioration, insulin resistance 1149
American Association of Clinical Endocrinologists (AACE) 559–561, 952
American College of Endocrinology (ACE) 518, 560
American Diabetes Association (ADA)
biomarkers/precision medicine 423–424
blood pressure 737
care aims 348–349
children 1013–1014
classification/diagnosis 23–24, 27
dietary factors 373
drug-induced diabetes 299
empowerment education 356–357, 917
epidemiology 58–59
exercise 397
history 19
hypoglycaemia 587, 591–592
insulin and insulin therapy 438
obesity 255
oral glucose lowering drugs 518, 524
pancreas 327
psychosocial aspects 937, 960
sexual function 792
transplantations 473
Type 1 diabetes 212, 219
AMIGO trials 525
amino acids
glucagon 99–101, 104–107
glucose metabolism 77–80
insulin action 113–114, 117–119
insulin function/secretion 86–89, 92–95
amphetamine 143–144, 957, 965–967, 1164
AMPK *see* adenosine 5'-monophosphate-activated protein kinase
AMPLITUDE-O trial 527, 543
amputations
lower-limb symptoms 32–33, 771–779
peripheral vascular disease 755, 757–762
sensorimotor polyneuropathy 655–658
amylin 222–223, 520, 529–530
amylin analogues 520, 530
amylin receptors 529–530
amyloidosis 222–223
amyotrophy 658
anaemia 407–408, 500, 525, 607, 650–651
anaerobic exercise 382–383, 398–400
anakinra 1131–1132
ANDIS (All New Diabetics in Scania) project 158–159
ANDIU (All New Diabetics in Uppsala) 158
androgen steroids 304, 314, 316–317
aneurysms
arterial disease 755, 762–765
retinopathy 629–630, 634–637
angiogenesis 1140–1142
angiography 635–636, 761
angiopathy 615–616, 621, 624
angiotensin (AT) 687–690
angiotensin-converting enzyme (ACE 2) 681, 687–690, 695, 886
angiotensin-converting enzyme (ACE) inhibitors
biomarkers/precision medicine 414–415, 422–423
heart failure 738–739
hypertension 707–708
macrovascular complications 681, 687–690, 695
nephropathy 648–649
neuropathy 665
Type 2 diabetes 70
angiotensin II 119, 668, 686–690, 707–708
angiotensin receptor blockers 422–423, 708
animal insulins 432, 437, 439, 441
animal studies
advanced glycation end-products 619–620, 685
APOE knockout mice 683, 691
β-cells defects 233–234
body weight 149–150, 262–263
enteropathy 798–799
gastrointestinal tract 798–799
gene therapy 1144–1151
genetics 15, 121–124
glucotoxicity 683
hypoglycaemia 582–583, 588
infections 880–881
insulin resistance 241–243
islet and metabolic regulation 99, 103, 107
microbiome 265–268
anion gap 1002–1003
ankle blood pressure 755–757, 762
ankle-brachial index (ABI) 542, 755, 1141
anorectal dysfunction 800–802
anorexia nervosa 943–947
antibiotics 49–50, 884, 888–894
foot problems 777–778
metabolic endotoxaemia 264–265, 268
neuropathy 673–674
skin infections 845
anticoagulation 729–730, 753
anticonvulsants 666
anti-depressants 151, 666, 782, 791
antiemetics 573, 801, 807, 1013
anti-fungal agents 299–300
antigen-specific therapy 133
anti-hypertensive agents
drug-induced diabetes 298

global burden of diabetes 34
macrovascular complications 695, 700, 703–709
NAFLD 835
nephropathy 648–650
pregnancy 1043
sexual dysfunction 782, 791
anti-microbial agents 300–301
anti-obesity medications 150–151, 256–258, 517, 552–554, 1164
anti-platelet therapy 34, 749, 752
anti-protozoal agents 299–300
anti-psychotic drugs 150–151, 295–297, 782, 791, 949–951
anti-retroviral therapy 151, 299, 878, 883–884
anti-thrombotic agents 750
Antithrombotic Trialists Collaboration 749, 752
anti-thymocyte globulin 1130–1131
anxiety disorders 907–918, 933–934, 938–942, 945–947, 1029–1030
aortic aneurysmatic disease 755, 762–765
APOE knockout (KO) mice 683, 691
apolipoproteins 243, 389, 424–425, 714, 715, 728
Apollonius of Memphis 22
apoptosis-inducing ligands 682, 692
appetite-regulation 142–152, 523, 529–530
Arabia 4, **15**, 64–65, 879
arachidonic acid derivatives 91
Aretaeus of Cappadocia *5*
Argentina 44
aristaless-related homeobox (Arx) 100
arms *see* upper limbs
arrhythmias 829–830
arterial disease 681, 688–690, 752–767, 771–775
abdominal aortic aneurysm 755, 762–765
amputations 755, 757–762
aortic aneurysmatic disease 755, 762–765
arm ischaemia 762
asymptomatic stage 755
atherosclerosis 755–767
blood pressure 755–757, 762–763
carotid artery disease 752–753, 755, 765–767
carotid stenting 766–767
claudication 755
coronary artery disease 681, 688–690
diagnosis 756–757, 760–761, 763, 765
foot disease 771, 773–775
hypertension 724, 729
incidence 755–756
infections 878–881, 893
interventions 758–760
ischaemic heart disease 724, 729
management 757–761, 763–766
mesenteric artery occlusive disease 761–762
non-healing ulcers 755
open surgical revascularization 759–760
pathophysiology 755, 760, 762–763
percutaneous transluminal angioplasty 758–759
peripheral 755–767, 771–776, 878–881, 893
prevention strategies 761
prognosis 757, 761, 763, 765
renal artery obstruction 761–762
renal artery stenosis 705
rest pain 755
screening 764
stem-cell therapy 1140–1142
stenting 766–767
surgical management 758–760
symptoms 760, 762–763
technical considerations 766
thrombosis 760–761
ulceration 755
artificial intelligence 444, 455
artificial pancreas 453, 457, 461, 464–465, 918
Arx *see* aristaless-related homeobox
Asia
see also South Asia
global burden 29–31, 35
Type 1 diabetes 42–47
Type 2 diabetes 56, 63–64, 67–69
aspergillosis 884–885
aspirin 752, 1075, 1077
Asymptomatic Carotid Atherosclerosis Study (ACAS) trial 766
asymptomatic carotid stenosis 766
Asymptomatic Carotid Surgery Trial (ACST) 766
AT *see* angiotensin
atherogenic dyslipidaemia 820, 825–831
atherosclerosis 681–695
angiotensin-converting enzymes 687–690
cardiovascular disease 534, 538, 541–548, 724–730
immune responses 692
ischaemic heart disease 724–730
oxidative stress 691–692
pathogenesis 681–695
peripheral vascular disease 755–767
RAAS 687–690
stroke 745, 747–748
Type 2 diabetes 534, 538, 541–548
UT II 691
vasoactive hormones 687–690
Atlas 58–59
ATP *see* adenosine triphosphate
atrial fibrillation 753
attention, cognitive function 922–927
atypical antipsychotics 297
atypical phenotypes 216–224
Australia 29–31, 42, 44–46, 50–51, 65
Austria 595, 960
autoantibodies 25, 203–213, 1125–1134
autoimmune disease 1046
autoimmune hepatitis 821–822
autoimmune polyglandular syndromes 317
autoimmune Type 1 diabetes
adults 217–219
antigen-2 203–204, 208
autoantibodies 203–213, 1125–1134
β-cell function 203–212, 1125–1134
biomarkers 206–207, 211–212
cellular autoimmunity 211–212
childhood 203–213
clinical onset peaks 203–213
diagnosis 212–213
environmental factors 203–210
epidemiology 204–206
future immunotherapies 1125–1136
GAD autoantibodies 203–213
genetic aetiology 207–210
haplogenotypes 203, 205–213
human leucocyte antigen genes 203, 205–213
humoral autoimmunity 212
immune checkpoint inhibitors 216–219
immunotherapies 1125–1136
insulin 203–213
islet autoimmunity 203–213
natural history 203, 205–206
pathogenesis 203–223
prevalence 203–205
screening 212–213
staging types 205–206
trigger biomarkers 211
virus aetiology 210–211
automated insulin delivery 431, 438, 444–446, 457, 464, 597
automated islet isolation 477
autonomic failure 586–587, 668
autonomic gastrointestinal dysfunction 797–798, 802–803, 806
autonomic neuropathy 655–658, 661–664, 669–674
classification and diagnosis 22
foot disease 772
gastrointestinal tract 798
hypoglycaemia 580–584
infections 878, 881, 888
insulin secretion/islet function 84, 89, 93–96, 101–102
sexual dysfunction 780–783, 788, 790
autonomic reflex testing 669–670
autosomal dominant family history 275–291
average daily risk range (ADRR) 452
Avicenna **4**, **15**
AWARD study 526, 648

BABYDIAB study 206–207
Bacillus fragilis 890
bacterial infections 838–839, 845, 848
bacterial overgrowth 796, 800–801, 806–807
bactericidal activity 878, 880–881, 888–892
bacteriuria 888
Bacteroidetes 261–263
balance cards 363–364
Baldwin, James 973
Bang, Ivar Christian 6
Bangladesh 64, 940, 988, 990–991
Banting, Frederick Grant 9–12, 431–432
Bardet-Biedl syndrome 198
bariatric surgery 146–147, 250, 255, 258, 551–557
body mass index 556–557
efficacy 555–556
monitoring diabetes 412
NAFLD 820, 832
pregnancy 1043–1044
referral pathways 556–557
barrier contraception methods 792
Barron, Moses 9
basal insulin delivery 434, 440–441, 459–464, 999, 1006
basal insulin replacement 103

basal metabolic rate 197–198, 201
baseline albuminuria 640–652
BASIL trial 759
Baum, John 14
BDL_G *see* biologically defended level of glycaemia
BDNF *see* brain-derived neurotrophic factors
BDNF signals, obesity 198
Beaser, Samuel 19
Beck Depression Inventory 789–790, 938
bedside foot disease screening 772–773
beef-derived insulin 10, 432
behavioural factors
  adolescents 907, 910–919, 1022–1030
  anxiety 907–918
  blood glucose 907, 912–916
  body weight 142–152
  children 907–915, 1014–1015
  cognitive behavioural therapy 908, 916–919
  complications 907–913
  counselling 907, 918–919
  depression 907–918
  diabetic ketoacidosis 907, 911
  discrimination 907, 911–912
  distress 908–919
  eating disorders 907, 910–915
  education 358–361, 908, 917–918
  emotional factors 908–918
  empowerment 908, 917
  environmental risk 908–909, 914
  family factors 908–919
  family therapy 908, 911, 916–919
  glycaemic control 907–918
  group therapy 907, 918–919
  hypoglycaemia 907–913, 917–918
  insulin delivery 918
  long-term complications 912–913
  management 907–919
  mindfulness-based therapies 908, 916–917
  mood aspects 910, 913–919
  novel technologies 918
  obesity 142–152
  patient education 358–361, 908, 917–918
  psychosocial aspects 907–921
  psychotherapy 908, 916–919
  quality of life 907–919
  retinopathy 907, 912
  self-management 907–919
  sleep 897–902, 908–910
  social determinants of diabetes 974–982
  stigma factors 907, 912, 917
  stress 908–919
  technology 918
  training aspects 908, 917–918
  transition to adulthood 1022–1030
  Type 1 diabetes 907–919
  Type 2 diabetes 907–919
  web-based CBT 908, 916
  well-being 907–917
Bell, Graham 15
Bensley, Robert 14
Berardinelli–Seip syndrome 288–291
Bernard, Claude 6–7, 128
Berson, Solomon 14–15
Best, Charles H. 10–12, 431, 432
β-blockers 295, 299, 706–708, 732, 739–741
β-islet cells
  amylin 520, 529–530
  autoantibodies 203–212, 1125–1134
  chronic stimulation 231–232
  defects 225–237
  destruction 25, 41, 203, 206, 261, 268–269
  dysfunction 128–130, 136–137, 225–237, 275–287
  failure 13, 26, 227–230
  gene therapy 1147–1148
  genetics 157–158, 190–193
  glucagon 99–107
  glucose metabolism 77–78
  hyperglycaemia 230–232
  hyperlipidaemia 230–231
  hypoglycaemia 579–588, 593
  incretin hormones 232
  insulin action 111–112, 116–124
  insulin secretion 84–96
  insulin therapy 432, 436, 438–439
  mass 229–230, 233–234
  metabolic regulation 99–107
  monogenic diabetes 275–291
  obesity 250, 252–255
  oral glucose lowering drugs 492–494, 501–504, 508–511
  physical activity 389–390, 396
  regeneration 1148
  replacement therapies 473–477, 485–488
  reprogramming 1147–1148
  stem-cell therapies 1137–1143
  subunits 112–114
  Type 1 diabetes 203–212, 389–390, 1125–1134
  Type 2 diabetes 13, 26, 157–158, 190–193, 225–237, 396, 1156–1160
BGAT *see* Blood Glucose Awareness Training
bicarbonate 607
Bifidobacterium 268, 1156
biguanides *see* metformin
bile acids
  insulin secretion 95
  microbiome 261, 267–268
  sequestrants 493, 496–498, 517, 717
biliopancreatic diversion 555–556
binge eating disorder 943–947
biologically defended level of glycaemia (BDL_G) 128, 135–139
biomarkers 414–428
  angiotensin receptor blockers 422–423
  autoimmune Type 1 diabetes 206–207, 211–212, 1113–1115
  cardiovascular disease 414–418, 422–426
  complications 414, 418, 423
  genetics 414–426
  glycaemic management 414–420, 425–426
  glycated haemoglobin 415, 417–422, 425
  hypercholesterolemia 414, 423–425
  hyperglycaemia 414, 417–419
  immunotherapies 1113–1134, *1135*
  kidney diseases 414–426
  metformin 418–420
  MODY 279, 417–418
  monogenic diabetes 414–418, 426
  neonatal diabetes 417
  pathophysiology 414–417, 426
  pharmacogenetics 414–416, 424
  precision medicine 414–428
  proteins 414–426
  research directions 425–426
  Type 1 diabetes 206–207, 211–212, 414, 418, 423, 426, 1113–1135
  Type 2 diabetes 414–426
biosimilar insulin therapy 435, 437, 540
biphasic insulin 372
bipolar affective disorder 933–934, 947–948
birth weight 57
black toe 330, 336
bladder cancer 508, 539, 868, 874–875
bladder dysfunction 673
blindness *see* retinopathy
blood glucose
  see also continuous glucose monitoring; glycaemic management; self-monitoring blood glucose
  adolescents 1019–1027
  ambulatory profiles 452–457
  behavioural factors 907, 912–916
  biomarkers 414, 417–421
  brain control sensing 130–134
  children 999–1014
  diabetes classification and diagnosis 23–25
  diabetes monitoring 404–412
  dietary factors 368–373, 376
  education 354, 362
  end-of-life care 1085, 1088–1092
  exercise 398
  frequency of measurements 445–446
  indirect sensing 134–135
  infections 878, 881–883, 893–894
  in-hospital treatments 574
  insulin secretion 95–96
  insulin therapy 444–457, 459–468
  measurements 408–410, 445–446
  monitoring 347–348, 404–412, 444–457, 592–594
  monogenic diabetes 275, 280–282
  nephropathy 640, 645–652
  novel insulin technologies 444–468
  oral glucose lowering drugs 492–518
  outcome assessments 451–457
  patient education 354, 362
  physiological changes 130–134
  physiological lag 449–450
  pregnancy 1034–1040, 1044–1049, 1056–1062
  psychosocial aspects 907, 912–916
  quality 445–446
  self-management 915–916
  steroid therapies 574
  transition to adulthood 1019–1027
  travel 968–969
  Type 1 diabetes 398, 411
  variability 452–454
Blood Glucose Awareness Training (BGAT) 917
blood pressure
  see also hypertension
  biomarkers/precision medicine 414–416, 418, 421–423
  children 1015
  elevation in children 1015
  historical perspectives 17–18
  hormone replacement therapy 793
  ischaemic heart disease 724, 729

nephropathy 640–652
obesity 250, 254–256
peripheral vascular disease 755–757, 762–763
blurred vision 333
body fat distribution 197–199
body mass 261–263
body mass index (BMI) 142, 146–151, 556–557
clinical presentation 331
obesity 197, 201, 250–258
Type 2 diabetes 56, 63–64, 67, 70
body temperature 134–135
body weight 142–154, 197–201, 250–258
see also obesity
adipose tissue 144–145, 197–199, 250–254
adolescents 1027–1029
anti-diabetic oral agents 553–554
appetite-regulation 142–152
bariatric surgery 146–147, 250, 255, 258, 551–557
biliopancreatic diversion 555–556
biological control 142, 149–152
body mass index 142, 146–151, 556–557
caloric restriction 255–256, 368, 370–374, 551–553
cardiovascular risk factors 551–555
clinical presentation 333
cognitive factors 142–143, 145
control of 142–154
dietary factors 142–152, 368–376, 551–557
duodenal switch 555–556
emotional factors 142–145
energy homeostasis 142–152, 197–199
gain/loss 142–154, 197–201, 250–258
biological mechanisms 142, 149–152
care aims 346, 348
children 999, 1001, 1008
clinical presentation 330–333, 336–337
control of 142–152
dietary factors 368–372, 375–376
drug-induced diabetes 295–297
ease of 142–154
genetics 197–199, 201
glucose homeostasis 136–139
hyperglycaemia 348
hypersecreting endocrine disorders 310, 313–314, 316–317
metabolic surgery 551–557
monogenetic diabetes 291
NAFLD 820–822, 825–828, 831–835
nephropathy 650
neuropathy 664
oral glucose lowering drugs 492–493, 499–501, 504–513, 516–517
pancreatic diseases 319, 323–328
intestinal microbiome 145
leptins 147, 199–200
lifestyle factors 551–552, 556–557
management 142–154, 250–260, 551–557
melanocortin-signalling 147, 199–200
mental disorders 933–952
metabolic alteration 145–146
metabolic surgery 551–558
microbiome 145, 261–263
nephropathy 650
neuropathy 655–658, 664, 670, 673
neurotransmitters 144
non-insulin parenteral therapies 520–530
one anastomosis gastric bypass 555–556
oral glucose lowering drugs 492–494, 497–501, 504–518
pharmacotherapies 150–151, 256–257, 517, 552–554
physiological regulators 142–151
pregnancy 1034–1043, 1046–1066
proopiomelanocortin 147, 199–201
single-minded 1 transcription factors 147–148, 200
sleeve gastrectomy 146–147, 554–556
surgical management 146–147, 551–557
transition to adulthood 1027–1029
twin studies 197–198
Type 2 diabetes 535–541, 547–548, 551–557, 1164
bolus calculations 351, 445, 459–464, 467, 1006
bone chemistry 650–651
bone density 390, 396, 508, 556, 793, 859–863
bone disorders 853–866
see also musculoskeletal disease
bariatric surgery 556
carpal tunnel syndrome 855–856
Charcot joint 856–857
cheiroarthropathy 853–854
diffuse idiopathic hyperostosis 858–859
Dupuytren's contracture 855
fibroproliferative disorders 853–856
fractures 793, 859–863
frozen shoulder 854–855
gout 857–858
infections 893
joint disorders 853–858
limited mobility 853–854
osteoarthritis 858
osteoporosis 390, 396, 793, 859–863
rheumatoid arthritis 858
skeletal disease 858–863
stenosing tenosynovitis 855
trigger finger 855
Bornstein, Joseph 14–15
Bottazzo, GianFranco 13
botulinum toxin 665–666, 674, 807
Bouchardat, Apollinaire 9
bovine insulin 50
brachial plexus injury 1040
brain
see also cognitive function; neuropathy
antidiabetic oral agents 138–139
blood glucose levels 130–137
body temperature 134–135
energy balance 131–133, 135
GLP-1 129, 138–139
glucagon 105
glucose homeostasis 128–139
glucose metabolism 77–78, 81–82
hypoglycaemia 135–137, 579–588
insulin secretion 93
metformin 139
normoglycaemia restoration 137–139
thermoregulation 134–135
brain-derived neurotrophic factors (BDNF) 147–148
Brazil 29, 44, 62, 887
breast cancer 745, 793, 868, 871–873
breastfeeding 1049, 1065
British colonies 975
British Diabetic Association (now Diabetes UK) 18–19
British Obesity Metabolic Surgery Society guidelines 552
bromocriptine 496, 498, 516–517
bronzed diabetes 325
brown adipose tissue 105–107, 117, 123–124, 134–135, 1149–1150
Brown-Séquard, Charles-Édouard 8
buffalo hump 310
bulimia nervosa 943–947
bullosis diabeticorum 840
bupropion 256, 553
Burkholderia pseudomallei 882
burnout 1019–1020, 1026, 1029

C2, C3, C4 & C5 complement systems 622–624
cabergoline 306–307
cachexia 658
calcific pancreatic diseases 319–324
calcific uraemic arteriolopathy (calciphylaxis) 844
calcineurin inhibitors 295, 301
calcium 91–92
calcium channel antagonists 707
calcium channel blockers 665
calculi 319, *322*
callus accumulation 774
calmodulin-dependent kinases (CaMK) 91–92
calories 146, 255–256, 368, 370–374, 551–553
Calvi, Charles Marchal de 8
Cambodia 67, 114
CaMK *see* calmodulin-dependent kinases
cAMP *see* cyclic adenosine monophosphate
Canada
adolescents 1024, 1027, 1031
gestational diabetes mellitus 1054–1056
global burden 29
infections 879
social determinants of diabetes 975–978
Type 1 diabetes 44
Type 2 diabetes 61
canagliflozin 492, 496, 511–513, 544–545
canakinumab 1131–1132
cancers 867–877
anti-diabetic oral agents 867–868, 871–876
biases 868–870
clinical outcome 875
confounding 868
detection time bias 868–869
diagnosis 875–876
epidemiology 867–876
ethnicity 868
gestational diabetes mellitus 871
global burden of diabetes 34
α-glucosidase inhibitors 873
hyperglycaemia 867, 871–872, 875–876
hyperinsulinaemia 867, 871–872, 875–876
incidence 869
incretin drugs 867, 872–873, 875–876
insulin 867–876
management 867–876
metformin 867–868, 872–876

cancers (*cont'd*)
mortality 867–876
NAFLD 820, 823–835
obesity, genetics 197
onco-diabetology 867, 875–876
oral health 810, 817
pathophysiology 867–868, 875–876
pharmacology 872–875
physical activity 390, 396
pioglitazone 873–874
risk factors 867–876
rosiglitazone 873–874
screening 867–868, 875–876
SGLT-2 inhibitors 873
smoking 868
thiazolidinediones 867, 872–874, 876
time biases 868–870
tumour biology 867, 875
Type 1 diabetes 390, 868, 870–871
Type 2 diabetes 396, 867–876
Candida albicans 845–846, 881–882
candidal infection 810, 816, 845–846, 878, 881–882, 890–891
cannabis 966–967
cannulas, types of 468–469
CANVAS trial 415, 544, 547, 726
CAP *see* controlled attenuation parameter
capillaries
blood glucose 404, 409, 444–457
pathogenesis 615–616, 624
retinopathy 629–631, 637
CAPN10 gene on chromosome 10 encoding calpain 10 157, 160, 167, 190, 228
capsaicin 667
carbohydrates
adolescents 1019–1020, 1024
children 1008, 1010
Cushing syndrome 309–310
dietary factors 368, 371–376
gestational diabetes mellitus 1050
hormonal contraception 792
hyperglycaemia 372
hypoglycaemia 579–582, 588, 594–596
insulin 368, 372
metabolism 78–81, 250, 255, 309–310
oral glucose lowering drugs 493, 496–498, 503–504, 514–516
physical activity 382, 392, 399–400
quality/quantity 372–373
Type 2 diabetes 534, 537
carbon monoxide 85–86
carboxyl ester lipase (CEL) 219–220, 288
carcinomas 319–320, 324–327, 820, 823–835
cardiac autonomic neuropathy 669–671
cardiac diseases 829–830
cardiac embolization 747
cardiac function tests 705
cardiac regenerative medicine 1140–1141
cardiac resynchronization therapy (CRT) 740–741
CardioMetabochip 167
cardiorespiratory function 250, 255
cardiovascular autonomic reflex testing 669–670
cardiovascular disease
atherosclerosis 534, 538, 541–548, 724–730
biomarkers 414–418, 422–426
body weight 142, 150, 551–555
care aims 343, 347–350
cholesterol 713–721
cognitive function 931
complications 615–616, 622–626, 681–696, 700–710, 713–723
dementia 931
depression 936–937
dietary factors 368–376, 716, 718–719
dyslipidaemia 695, 713–720
fibrates 713–721
future drug therapies 720
global burden of diabetes 32–34
GLP-1 523
glucose levels 713–714
glycaemic management 713–716
heart failure 732–742
high-density lipoproteins 713–721
hyperglycaemia 713, 715, 718
hypertension 700–710, 713–715
hypoglycaemia 590–591
infections 878–894
insulin action 111, 119
ischaemic heart disease 724–730
islet cell transplantation 473, 476–487
low-density lipoproteins 713–721
mortality 713–715, 718–721
multidisciplinary teams 1097–1104
NAFLD 720–721, 820–821, 825, 828–830, 833–834
nephropathy 640–652, 713–715, 718
neuropathy 615–616, 622–626, 655–656, 659, 669–671
niacin 718
obesity 142, 150
omega-3 fatty acids 718–719
oral glucose lowering drugs 492–518
outcome trials 520, 523–530, 541–545, **1076**
pathogenesis 615–616, 622–626, 681–696
PCSK9 inhibitors 717
PDE5 inhibitors safety of 785–786
physical activity 382–384, 389, 393–395, 398
precision medicine 414–418, 422–426
pregnancy 1034–1035, 1047–1063
protection 689–690
RAAS inhibition 689–690
risk factors 551–555, 713–730, 1034–1035, 1047–1063, 1097–1104
sexual dysfunction 780–786, 790–793
sleep 900–901
smoking 713, 720
statins 713–721
stem cell therapy 1140–1142
triglycerides 713–721
Type 1 diabetes 383–384, 713–720
Type 2 diabetes 393–394, 534–548, 713–720
whole pancreas transplantation 473, 476–487
cardioverter-defibrillator 740
CARDS study 695, 716
care
see also end-of-life care; healthcare
aims of 343–353
ambassadors 1023, 1033
delivery of 18–20, 1109–1118
homes 1072–1074, 1077–1078, 1081–1082
models 1097–1101, 1107–1121
organization 652
plans 492–493, 518, 1082
teams 343–365, 926–933, 938–939, 946–947, 1097–1105
carer involvement 926
Caribbean 29–30, 62, 69, 559, 644, 707, 745–746, 988–990
caries 810, 816–818
CAROLINA trial 542, 726, 737, 742
β-carotene 375, 1155
carotid artery disease 752–755, 765–767
carotid endarterectomy 752–753
carotid intima-media thickness 309, 481, 501, 748
carotid revascularization 767
carotid stenosis 765–766
carotid stenting 766–767
carpal tunnel syndrome 855–856
cascade signalling 114–124
cataracts 338
catecholamines 82, 304, 312–314, 583–584, 595–596
CBT *see* cognitive behavioural therapy
CCK *see* cholecystokinin
CCM *see* corneal confocal microscopy
CD2 blockade 1129
CD3 blockade 1128–1129
$CD4^+$ cells 1125–1130
$CD8^+$ positive T cells 1125–1130
CD14 265–266
CD20 blockade 1131
CD80 & CD86 blockade 1129–1130
CDKAL1 genes 157, 190, 193
CDKN2A/2B genes 157, 190
CEL *see* carboxyl ester lipase
celiac disease 25, 800
cell death 487
cell-mediated immunity 878, 880
cellular autoimmunity 211–212
cellular encapsulation 487–488
cellular glucocorticoid inhibitors 1154
cellulitis 845–846, 884, 891–893
CEMACH study 1035, 1038–1041
Center for Epidemiologic Studies Depression Scale 938
Central America 29–30, 44–45, 62, 989
Central Asia 32, 69
central nervous system (CNS) 100, 105, 128–144
see also neuropathy
central sleep apnoea (CSA) 898, 900
central vision 629–630, 633–634, 637
cerebral oedema 1003–1004
cerebrovascular disease 745–754
see also stroke
CETP *see* cholesterol ester transfer proteins
CGM *see* continuous glucose monitoring
cGMP *see* cyclic guanosine monophosphate
Chanarin–Dorfman syndrome 243
change-based care relationships 358, 363–364
Charak **4**, *5*
Charcot neuroarthropathy 657, 771, 778, 856–857
cheiroarthropathy 853–854
chemoattractant molecules 1126
chemotaxis 845, 878, 880–881

Chen Chuan **4**
chenodeoxycholic acid 820, 835
Chevreul, Michel 6
children 999–1018
  Addison disease 1016
  ambulatory care 1004–1006
  basal-bolus injection regimens 999, 1006
  behavioural factors 907–915, 1014–1015
  blood glucose 999–1014
  blood pressure 1015
  carbohydrates 1008, 1010
  cerebral oedema 1003–1004
  clinical presentation 1001–1004
  coeliac disease 1016
  continuous glucose monitoring 999, 1004–1015
  dehydration 999, 1001–1004, 1012–1013
  dextrose 1011
  diabetic ketoacidosis 999–1007, 1010
  diagnosis 999–1006, 1012–1016
  dietary factors 376
  dyslipidaemia 1015
  education 999, 1001, 1004–1008
  exercise 596, 999–1000, 1004–1010
  family factors 1001–1008, 1012–1015
  fluids 999, 1001–1004, 1012–1013
  genetics 197–201, 1001–1002
  glucagon 1011
  glycaemic management 999–1000, 1003–1015
  glycated haemoglobin 999–1001, 1004–1007, 1011–1016
  goals of treatment 1013–1014
  hyperglycaemia 999–1009, 1012–1013
  hyperglycaemic hyperosmolar syndrome 1004
  hypertension 1015
  hypoglycaemia 579–580, 590, 594–597, 999, 1003–1016
  initial treatments 1001–1004
  insulin therapy 999–1002, 1005–1014
  ketones 1010, 1012–1013
  Kussmaul breathing 999, 1001–1002
  management 999–1016
  microalbuminuria 1015
  monogenic diabetes 1002
  multidisciplinary teams 1102–1103
  neuropathy 1016
  nutrition 999–1001, 1005, 1008
  obesity 197–201, 250, 252
  pathogenesis 203–213
  polydipsia 999, 1001, 1004
  polyuria 999, 1001, 1004
  psychological support 1014–1015
  psychosocial aspects 907–915, 1005–1008, 1014–1015
  retinopathy 1015–1016
  risk factors 1015–1016
  schools, management in 1005–1006
  screening 999, 1005, 1008, 1012, 1015–1016
  self-management 999, 1005, 1013–1015
  sick-day management 1012–1013
  sleep 901
  spectrum of diabetes 999–1011
  subcutaneous insulin 1003–1007
  technology aspects 999–1015
  telemedicine 999, 1004–1005
  thyroid disease 1016
  Type 1 diabetes 41–52, 203–213, 999–1016
  Type 2 diabetes 999–1004
  weight loss 999, 1001, 1008
Chile 44, 62, 966
China
  end-of-life care 1085
  genetics 157–158
  global burden of diabetes 29–32, 35
  infections 337–338
  Type 1 diabetes 42–44, 46
  Type 2 diabetes 55, **60**, 66–68
China Da Qing Diabetes Prevention Outcome Study 390, **391**
chlorpromazine 849
chlorpropamide 233, 494, 501–504, 850
Chlouverakis, Costas 18
cholecystitis 890
cholecystokinin (CCK) 95, 144
cholesterol
  see also high density lipoproteins; low-density lipoproteins
  biomarkers/precision medicine 414, 423–425
  cardiovascular disease 713–721
  dietary factors 374–375
  gene therapy 1149
  hypoglycaemia 597
  ischaemic heart disease 724, 727–729
cholesterol ester transfer proteins (CETP) 424–425
cholinesterase inhibitors 931
chromaffin cells 304, 312–314
chronic complications
  adolescents 1027–1028
  arm ischaemia 762
  care models 915, 1100
  costs 36
  historical perspectives 13–14
  hyperglycaemia 331
  immunosuppression 487–488
  kidney disease 534–537, 541–548, 640–652, 734, 828–831, 1142–1143
  pancreatitis 319–328
  stimulation 231–232
cibinetide 668
ciliary disorders 198
circadian control/patterns 130, 149–150
cirrhosis 820–835
  see also non-alcoholic fatty liver disease
classical diabetic nephropathy 641–643
classification of diabetes 22–27
classified controlled drugs 965
claudication 755
clear-cell syringomas 847
clinical decision tools 407, 1060, 1063
clinical presentation overview 330–339
clinical trials
  see also individual trials
  biomarkers/precision medicine 414–415, 422–426
  blood glucose 451–454, 466
  body weight 255–257, 551–553
  dapagliflozin 544–546
  gene therapy 1145, 1148–1150
  high density lipoproteins 683–685
  history 10, 18, 26, 34, 68–70
  hyperglycaemia 682
  inflammation 1132–1133
  insulin therapy 435–436, 459, 463–469
  intestinal microbiome 265–267
  metabolic surgery 551–553
  pancreas transplantation 474–477, 485
  physical activity 390
  pregnancy 1043–1045, 1050
  psychosocial aspects 915–918, 939, 950, 980
  stem-cell therapy 1140–1142
  Type 2 diabetes prevention 390, 392
clinic visits 347–352
closed loop insulin delivery systems 444–445, 453–457, 579, 593, 597, 1007–1008, 1034–1035
Clostridium spp. 845, 890
clot retrieval 750
CNS *see* central nervous system
cocaine 966
Cochrane Database systematic review 297
co-creation/co-design methods 1115–1116
coefficient of variation (CV) 452, 457
coeliac disease 1016
cognitive behavioural therapy (CBT) 908, 916–919
cognitive function 922–932
  Alzheimer's dementia 924–926, 931
  attention perspectives 922–927
  body weight 142–145
  cardiovascular disease 931
  comorbidity 923–924, 931
  definitions 922–923
  delirium 926–927
  dementia 922–932
  diagnosis 922–932
  executive function 922–930
  global burden of diabetes 35
  glycaemic control 922–926
  hyperglycaemia 922–926
  hypoglycaemia 924–926, 930–931
  impairment 923–932
  language 922–930
  medication factors 922–932
  memory 922–929
  morbidity 923–924, 931
  neuropsychologists 929
  occupational therapists 927–928
  older patients 1072–1082
  pathogenesis 924–925
  physiotherapists 927
  processing speed 922–924, 927
  psychosocial aspects 922–932
  screening 922–925, 929–931
  self-management 922–932
  social isolation/support 922–923, 930–932
  targeted management plans 926
  Type 1 diabetes 922–925
  Type 2 diabetes 922–927, 930
  vascular disease 924–931
  visual perception 922–924, 927–930
colesevelam 493, 496, 498, 517
Collaborative Atorvastatin Diabetes Study 650, 695, 716
Collip, James B. 10–12, 432
Colombia 44, 62
colonialism 975–982
colonic dysfunction 673

colorectal cancer 820, 828
combination therapies
  contraception 295, 297–298
  hypertension 700, 703–704, 706–709
  insulin 440–441
  neuropathy 667
communicable diseases 1108, 1110–1111, 1113–1117
community care
  health workers 1105
  insulin therapy 441–442
  provision 1097–1105
community pharmacists 1104
comorbidity
  cognitive function 923–924, 931
  dementia 923–924, 931
  heart failure 732–740
  LMIC care models 1110–1111
  mental disorders 933–938, 941–947
  nephropathy 640, 648–651
  obesity 142, 147–148, 150–151, 547
  older patients 1072–1082
  oral glucose lowering drugs 492, 494
  Type 2 diabetes 534, 538, 547–548
complement system 622–624
  see also innate immunity
comprehensive foot exam 772, 1082
computed tomography (CT)
  bone disorders 861
  cancers 871
  enteropathy 798, 804
  foot disease 777
  hypersecreting endocrine disorders 312
  infections 884, 889–891
  NAFLD 822–823
  neuropathy 656
  pancreatic disease 319
  peripheral vascular disease 761, 763
  stroke 750–752
CONGA *see* continuous overlapping net glycaemic action
congenital generalized lipodystrophy 288–291
congenital malformation 1034, 1037–1039, 1042–1044
congenital rubella syndrome 49
connective tissue growth factor (CTGF) 621
CONSENSUS trial 739
constipation 796, 800–808
consultations 345–346
continuity of care 1114–1115, **1118**
continuous-acting GLP-1RA 525–526
continuous glucose monitoring (CGM) 404–405, 410–412, 444–457
  adolescents 1019–1021, 1026–1027
  alarm setting 451
  analytical aspects 444, 449–452, 457
  automated insulin delivery 457
  calibration 449
  children 999, 1004–1015
  data visualization 444, 451–454
  future perspectives 455–457
  hypoglycaemia 579, 583, 592
  insulin therapy 444–470
  islet cell transplantation 473
  outcome assessments 451–457
  performance requirements 448–449
  physiological lag 449–450
  practical issues 449–451
  pregnancy 1035, 1044–1045
  pump devices 459–470
  sensor calibration 449
  skin issues 451
  software solutions 444–445, 452–455
  standardized analysis 444, 449–452, 457
  transition to adulthood 1019–1021, 1026–1027
  trend arrows 450–451
  visualization 444, 451–454
  whole pancreas transplantation 473
continuous IV insulin infusion 1003
continuous overlapping net glycaemic action (CONGA) 452
continuous subcutaneous insulin infusion (CSII)
  artificial pancreas system 464
  basal delivery 459, 461–464
  basal rates/patterns 459, 461–463
  bolus advisors 459, 463–464
  dawn phenomenon 462–463
  end-of-life care 1090–1091
  in-hospital treatments 574
  islet cell transplantation 473
  pregnancy 1035, 1046–1049
  sensor-augmented smart pump therapy 464
  whole pancreas transplantation 473
contraception
  adolescents 1027
  drug-induced diabetes 295, 297–298
  pregnancy 295–298, 780, 791–792, 1049
  sexual health 295–298, 780, 791–792
  transition to adulthood 1027
controlled attenuation parameter (CAP) 822
controlled drugs 957, 965–967
Copenhagen City Heart Study 746, 748
CORAL study 761
corneal confocal microscopy (CCM) 662–663
coronary artery disease 681, 688–690
Coronary Drug Project 718
coronary syndromes 334–335
corpus cavernosum 673–674, 780–781, 784–787
corrected sodium 1002–1003
corticosteroids 82, 295, 301
corticotroph adenomas 311
cortisol levels 310
Corynebacterium minutissimum 845
costs of diabetes 35–37
cotton-wool spots 335
counselling 359–361, 907, 918–919
counter-regulatory stress hormones 602, 608–610
Covid-19 pandemic
  clinical presentation 337–338
  diabetes and infections 878–879, 882, 886
  ethnicity aspects 987–988, 991–993, 997
  LMIC care models 1110–1111
  polymerase chain reaction test 49, 52
COX *see* cyclooxygenase
C-peptides 86–88, 112, 216, 218–219
cranial neuropathy 658
C-reactive proteins 279, 560, 624, 777, 814, 821–822, 883, 1078
creatinine 640–642, 645–650
CREDENCE trial 545
crossing time zones 968
Crowfoot, Dorothy (Hodgkin, Dorothy) 14–15
CRT *see* cardiac resynchronization therapy
CSA *see* central sleep apnoea
CSII *see* continuous subcutaneous insulin infusion
CT *see* computed tomography
CTGF *see* connective tissue growth factor
CTL *see* cytotoxic T lymphocytes
Cuatrecasas, Pedro 15
Cuba 61, 254
Cudworth, Andrew 13
cultural aspects 987–998
  cultural competence 990–997
  cultural sensitivity 990–996
  definitions 988
  dietary habits 992
  discrimination relationship 992
  education 362–364, 994
  ethnicity/race/religion 987–997
  exercise 992
  fasting and feasting 994–995
  impact on care 992
  language barriers 988, 996
  lifestyle factors 992, 994–995
  migration 988, 991
  physical activity 992
  pilgrimage 994–995
  research priorities 995–996
  socioeconomic status 987–988, 991–992
  South Asian populations 990–992, 994
  taboos and barriers 991
Cushing syndrome 304, 308–312
custody, social aspects 956, 962
cutaneous manifestations 838–853
  see also skin
CV *see* coefficient of variation
cyclic adenosine monophosphate (cAMP) 91–95, 99–106, 116–124, 228, 1156–1157
cyclic guanosine monophosphate (cGMP) 228, 780–781, 784–786, 791
cyclooxygenase (COX) 91
cyclosporine 295, 301
cystic fibrosis 319–320, 327–328, 1036
cystitis 878, 889–891
cystopathy 674
cytokine interferons 1126, 1128
cytokines 615, 619, 621–622, 625
cytotoxic T cells 203, 211, 1148–1149
cytotoxic T lymphocytes (CTL) 216, 218, 1129–1130
Czechia 484, 748, 1085

DAFNE program 372, 917
DAG *see* diacylglycerols
DAISY study 205–207, 210
dapagliflozin 70, 492, 496, 511–513, 544–546
DASH diet 369–370, 374–375, 1065
data visualization 444, 451–454
DAWN2 study 36–37, 351–352, 362, 911, 913, 915
dawn phenomenon 438, 462–463
DAWN study 351, 750, 913
daytime sleepiness 901
DCCT trial
  cardiovascular disease 714–715, 725, 749

care aims 348
children 1012–1014
classification/diagnosis 23–24
genetics 192
glucose monitoring 444
history 17
hyperglycaemia 682–683
hypoglycaemia 589–590, 595–597
insulin 431, 438, 461
microvascular complication pathogenesis 616–619
monitoring aspects 404–406, 444
nephropathy 643, 646–647
neuropathy 664, 670–671
pregnancy 1039–1041
psychosocial aspects 910, 913, 958
transplantation 473
deafness 158, 291
death and end-of-life care 1085–1094
death-in-bed syndrome 473
debridement 776
decretins 95
deeper soft tissue infections 892–893
defective glucose counter-regulation 579, 582–587
defibrillators 740
DeFronzo, Ralph 13
dehydration 999, 1001–1004, 1012–1013
see also fluids
delayed hypoglycaemia, children 1010
delirium 926–927
delivery and labour in pregnancy 1048–1049
dementia 922–932
cardiovascular disease 931
carer involvement 926
clinical management 926–932
comorbidity 923–924, 931
delirium 926–927
long-term impairments 926–927
management 926–932, 1079–1080
morbidity 923–924, 931
multidisciplinary teams 926–931
neuropsychologists 929
occupational therapists 927–928
older patients 1072–1082
pathogenesis 924–925
physiotherapists 927
risk factors 1079
self-management 925–932
short-term impairments 926–927
targeted management plans 926
vascular disease 924–931
Democratic Republic of Congo 1108, 1112
DEND (developmental delay, epilepsy, and neonatal diabetes) 158, 283–284
Denmark
global burden 33
infections 879
psychosocial aspects 909, 949, 960
Type 1 diabetes 42–45, 55
Type 2 diabetes 62–63
dental health *see* oral health
depression 907–918, 933–942, 945, 947–949
biological mechanisms 936–937
body weight 151
cardiovascular disease 936–937
definitions 934
diagnosis 934, 938
epidemiology 934–936
glycaemic management 936–939
hyperglycaemia 936–937
hypoglycaemia 936–939
likelihood of diabetes 936
management 937–939
mechanisms linking diabetes 936–937
medication factors 938–939
obesity 151
older patients 1072, 1074, 1079, 1082
pharmacotherapy 938–939
psychological treatments 938
screening 938
sleep 897, 899–902
social aspects 907–918, 933–942, 945, 947–949
transition to adulthood 1029–1030
Type 2 diabetes 57
dermatophytosis 846
dermopathy (shin spots) 842
DESMOND programme 363, 917, 994
developmental delay 198–200
developmental origins of health and disease hypothesis 192
development stages
adolescent transition to adulthood 1020–1025
drug therapies **1155**
retinopathy 629–633
DEVOTE 541
dextromethorphan 668
dextrose 1011
diabetes, definitions 22, 58–59
diabetes classification 22–27
Diabetes Intervention Accentuating Diet and Enhancing Metabolism (DIADEM-I) 256
diabetes mellitus
see also specific conditions
classification and diagnosis 22–26
history 3–21
insulin therapy 438–442
social aspects 58
Diabetes Prevention Program (DPP) 371, 390–392, 501, 536, 664, 979, 981, 1065, 1076
Diabetes Remission Clinical Trial (DiRECT) 255, 551–552
diabetes self-management education and support (DSMES) 355–365
diabetes spectrum 158
diabetes syndemic 252
Diabetes UK 19, 255, 369–370, 560, 791, 915, 917, 966, 1087–1088
diabetic bullae (bullosis diabeticorum) 840
diabetic epidemic history 977–978
diacylglycerol–protein kinase C pathways 622
diacylglycerols (DAG) 91–92
DIADEM-1 *see* Diabetes Intervention Accentuating Diet and Enhancing Metabolism
DIAGRAM consortium 167, 193
dialogue 356–358
dialysis 640, 648–651, 894
DIAMOND Study (Multinational Project for Childhood Diabetes) 42–45
diarrhoea 672–673, 796, 800–807
diazoxides 295, 301
DIDMOAD syndrome 288
dietary factors 368–382
see also nutrition
alcohol 375–376
body weight 142–152, 368–376, 551–557
carbohydrates 368, 371–376
cardiovascular disease 368–376, 716, 718–719
care aims 347
children 376
composition 150
cultural considerations 992
cystic fibrosis 328
disaccharides 373
energy balance 133–134, 368–376
exercise 376, 382–403
fats 79, 227, 368–375, 718–719, 834–835
fibre intake 373
folic acid 368, 376
gestational diabetes mellitus 1058, 1065–1066
lifestyle factors 368–371
macronutrient content 368, 371–375
microbiome 261–267
micronutrients 375
NAFLD 832, 834–835
nephropathy 640–641, 645–646, 649–652
neuropathy 664
obesity 142–152, 250, 254–258, 368–369, 371, 375–376
oral glucose lowering drugs 492–496, 501, 516–518
physical activity 376, 382, 390–400
pregnancy 368, 376, 1058, 1065–1066
salt 375
sleep 901
sodium 369–370, 375, 423, 649, 706–708
South Asian populations 992
starch fermentation 262
sterols 375
supplements 1155–1156
sweeteners 373–375
Type 1 diabetes 368, 371–376
Type 2 diabetes 56–59, 62–71, 240, 368–376, 1155–1156
dieticians 1104–1105
diffuse idiopathic skeletal hyperostosis (DISH) 858–859
DIGAMI study 334
digital lifestyle intervention methods 1065–1066
DILP *see* Drosophila insulin-like peptides
dipeptidyl peptidase-4 (DPP-4) inhibitors 492, 496–498, 500, 504, 508–511, 514
biomarkers/precision medicine 420
efficacy 511
heart failure 741
indications 510–511
ischaemic heart disease 726
islet and metabolic regulation 99
microvascular complications 615–616, 626
modes of action 509
pathogenesis 615–616, 626
pharmacokinetics 509–510
Type 2 diabetes 535, 537–542, 546–547, 1159–1160

DiRECT *see* Diabetes Remission Clinical Trial
direct glucotoxicity 683–684
direct renin inhibitors 708
disabilities 34–37
disaccharides *80*, 373
discharge, in-hospital treatments 573–575
discovery of insulin 9–11, 431–432
discrimination
  behavioural factors 907, 911–912
  body weight/obesity 151–152
  cultural relationship 992
  global burden of diabetes 37
  religion 992
DISH *see* diffuse idiopathic skeletal hyperostosis
disseminated granuloma annulare 838, 842–843, 847–848
distress 908–919, 1029
disulfide linked α subunits 111–113
diuretics 706
DIY-APS *see* do-it-yourself artificial pancreas system
DKA *see* ketoacidosis, diabetic
DNA methylation 157, 191–194
DNA transfer 1144–1146
Dobson, Matthew 4–6
do-it-yourself artificial pancreas system (DIY-APS) 464
Dolger, Henry 15
dominantly inherited progressive hyperglycaemia 275, 280–285
Doniach, Deborah 13
dopamine D2 receptor agonists 496, 498, 516–517
DPP-4 *see* dipeptidyl peptidase-4 inhibitors
DPP *see* Diabetes Prevention Program
dressings, wounds 776–777
driving 956–962
  hypoglycaemia 957–958
  licences 959–961
  retinopathy 947–949, 957
  statutory requirements 959–961
  visual impairment 947–949, 957
DROPLET trial 256
Drosophila insulin-like peptides (DILP) 128–129
Drucker, Dan 17
drug cessation 1046, 1088, 1091–1093
drug-drug interactions 301–302, 494, 498, 511, 514–516, 667, 888, 939
drug-induced diabetes 295–303
  β-adrenoceptor antagonists 299
  antifungal/antiprotozoal agents 299–300
  antimicrobial agents 300–301
  antipsychotics 295, 297
  antiretroviral therapy 299
  β-blockers 295, 299
  calcineurin inhibitors 295, 301
  combined oral contraceptives 295, 297–298
  corticosteroids 295, 301
  diabetic ketoacidosis 295, 301
  diazoxides 295, 301
  dysglycaemia 295, 300–301
  fasting glucose 295, 297–299
  fluoroquinolone-associated dysglycaemia 295, 300–301
  glucocorticoids 295–296
  glucose homeostasis 295, 298–301
  glycated haemoglobin 295, 297–299
  hormone replacement therapy 295, 298
  human immunodeficiency virus 299–300
  hyperglycaemia 295–302
  insulin resistance 295, 297–299
  insulin secretion 295–302
  insulin sensitivity 296–301
  lipodystrophy 295, 299–300
  management 301–302
  menopause hormone therapy 295, 298
  nucleoside reverse-transcriptase inhibitors 295, 299
  pancreatitis 295, 299
  pentamidine 299–300
  prevention strategies 301–302
  protease inhibitors 295, 299–300
  statins 295–296, 299
  thiazide-diuretics 295, 298–299
drug-induced metabolic changes 57
Drury, Ivo *19*
DSMES *see* diabetes self-management education and support
dual blockade 649
dulaglutide 526–529, 538–539, 542–543, 547
duodenal switch 555–556, 832
Dupuytren's contracture 855
DURATION study 525
dysglycaemia 99, 295, 300–301
dyslipidaemia
  cardiovascular disease 695, 713–720
  children 1015
  heart failure 733–734
  insulin resistance 242
  NAFLD 820, 825–831
  older patients 1075, 1077
dyspepsia 796, 800, 802–807
dysphagia 796, 802

early cell death 487
Early Treatment Diabetic Retinopathy Study (ETDRS) 656
EASD *see* European Association for the Study of Diabetes
East Asia 29–31, 35, 42, 56, 63–64, 67–69
eating disorders 907, 910–915, 942–947, 1029–1030
  behavioural factors 907, 910–915
  clinical presentation 945–946
  definitions 943
  detection 946
  DSM-5 criteria 943
  epidemiology 943–944
  management 946–947
  outcome impacts 944–945
  transition to adulthood 1029–1030
Ebers paprus 4
ECASS-III trial 750
economic costs
  foot disease 771
  global burden of diabetes 35–37
  Type 2 diabetes 68–71
ECST *see* European Carotid Surgery Trialist's Collaborative Group
ectopic fat storage 238, 240, 245–246
ectopic insulin production 1146
Ecuador 30, 1108
EDHF *see* endothelium-derived hyperpolarizing factor
Edmonton Obesity Staging System 251
Edmonton Protocol 477–478
education
  see also patient education
  adolescents 1019–1031
  children 999, 1001, 1004–1008
  end-of-life care 1085, 1090, 1093
  ethnicity 994
  glycaemia 437–438
  hypoglycaemia 579, 587–588, 592–596
  in-hospital treatments 564
  insulin therapy 437–438
  LMIC care models 1116
  multidisciplinary teams 1098–1099, 1101–1105
  self-management 354–365, 1098–1099
  South Asian populations 994
  transition to adulthood 1019–1031
efpeglenatides 526–529
eGFR *see* estimated GFR
elasticity losses 838, 840
elective surgery 571
electrical spinal cord stimulation 668
electrolytes 602, 604, 607, 609–610
elevated blood pressure 1015
ELISA test 205, 1016
ELIXA trial 526–527, 541–542
EMA401 668
embolectomy 761–762
emergency care aims 343, 351
emergency contraception 792
emergency surgery 574
emerging adulthood *see* transition to adulthood
EMMA program 363
emotional factors 142–145, 908–918
empagliflozin 492, 496, 511–513, 545–546
EMPARE-GOUTCOME, trial 415, 547
empathy 346–348, 357–359
emphysematous cholecystitis 890
emphysematous cystitis/pyelonephritis 878, 889–891
employment 36, 65, 252, 914–915, 961–962
empowerment approaches 354–367, 908, 917, 1019–1022
endarterectomy 752–753, 759–761, 765–767
endocrine disorders 99–107, 304–318, 782, 789
Endocrine Society Workgroups on Hypoglycaemia 591–592
end-of-life care 1085–1094
  advance care directive/plan 1085–1087, 1091
  algorithms 1088–1092
  blood glucose 1085, 1088–1092
  competency 1085, 1093
  diabetic ketoacidosis 1085–1090
  documentation aspects 1085–1088, 1091
  drug cessation 1088, 1091–1093
  education 1085, 1090, 1093
  family factors 1085–1091
  glucocorticosteroids 1091
  glycaemic levels 1085–1093
  glycated haemoglobin 1085, 1088, *1092*

Gold Standards Framework 1086–1088
healthcare professionals 1085–1093
holistic approaches 575, 1085–1093
hypoglycaemia 1085–1093
in-hospital treatments 575
insulin therapy 1085, 1087–1093
management 1086–1093
medication factors 1088–1091
mortality 1085–1087
nutrition 1091
palliative care/medicine 1086–1089, 1093
patient identification 1086
steroid therapies 575, 1091, 1093
withdrawing treatment 1088, 1091–1093
endogenous insulin secretion 438
endometrial cancer 34, 870
endophthalmitis 884–885
endothelial dysfunction 681–696, 780–783
endothelial progenitor cells (EPCs) 1138, 1141–1142
endothelin receptor antagonists 650
endothelin system 620–621, 681, 690–691
endothelium-derived hyperpolarizing factor (EDHF) 781
endovascular aneurysm repair (EVAR) 763–764
end-stage renal disease 33–34, 640–652
energy homeostasis 103–108, 131–135, 142–152
body weight 142–152, 197–199
brain control 131–135
dietary factors 368–376
exercise 197–199
gene therapy 1144, 1149–1150
heritability 197–199
islet and metabolic regulation 99, 103–108
energy intake 197
enteric drainage 474
enteric peptides 102
Enterobacteriaceae 776, 889, 892
enteroendocrine cell function 261, 266–269
enteropathy, *see also* gastrointestinal tract
enterotypes, microbiome 261–263, 265
enterovirus infections 49
enuresis 331
environmental factors
behavioural aspects 908–909, 914
body weight/obesity 142, 147–152
chemical risks 49–50
mental disorders 933–936, 941, 948–949
microbiome 261–263
psychosocial aspects 908–909, 914
psychotic disorders 949
social determinants of diabetes 973–974, 978–982
Type 1 diabetes 48–52, 203–210
Type 2 diabetes 57
EPAC *see* exchange proteins activated by cAMP
EPC *see* endothelial progenitor cells
epigenetic influences
body weight/obesity 147–152
genetics of diabetes 192
Type 2 diabetes treatments 1164–1165
epinephrine 579–588
equality aspects 973–981, 991, 1111–1112
erectile dysfunction 673–674, 780–793
clinical approaches 782–784
general advice 784
hypogonadism 786
investigations 783–784
management 782–788, 791–793
men 673–674, 780–790
neuropathy 673–674, 782
pathophysiology 781–782
physiology 780–782
primary care 788
smoking 783
specialist care 788
testosterone 781, 784–786, 790–791
women 673–674, 780, 788–793
ERK *see* extracellular signal-regulated kinases
ertugliflozin 492, 496, 511–513
eruptive xanthomas 839, 841
erythema multiforme 850
erythrasma 845
Escherichia coli 16, 263, 848, 889–890
estimated GFR (eGFR) 640–651
Estonia 44, 51
etanercept 1132
ethnicity 987–998
cancers 868
Covid-19 pandemic impacts 987–988, 991–992, *993*, 997
cultural aspects 987–997
definitions 987–988
epidemiology 988–990
exercise and physical activity 992, 994
fasting and feasting 994–995
health inequalities 991
hypertension 709
indigenous populations 973–981
NAFLD 820–821, 825–828
nephropathy 644
race, relationship of 987–997
religion 987–995
research priorities 995–996
social determinants of diabetes 973–976, 979–982
South Asian populations 987–997
taboos and barriers 991
Type 1 diabetes 46–47
Type 2 diabetes 29–30, 59–68, 987, 990, 997
Etzwiler, Donnell 19
EURODIAB ACE Study 42
EURODIALE study 336
EUROPA study 690
Europe
see also individual countries
autoimmune diseases 204, 212, 217–218
cancers 871, 874–875
cardiovascular disease 720
care aims 344, 348–349
cerebrovascular disease 745–747, 750
children 999
culture, ethnicity & religion 987–992, 996–997
foot disease 771, 774
genetics 157–160, 167, 190, 199
global burden 29–30, 32, 34–35
hypertension 109–110, 700, 704–705
hypoglycaemia 592, 595, 619
infections 882–883, 891
insulin therapy 435–440, 468
intestinal microbiome 263, 267
NAFLD 820, 824, 826
nephropathy 643–644, 662
non-insulin parenteral therapies 524–526
obesity 190, 199, 251, 255, 554
older patients 1073, 1078
peripheral vascular disease 755, 760, 764
psychological issues 935, 950
stem-cell therapy 1140
treatment in clinical practice 536–539, 541–543
Type 1 diabetes 42–52, 204, 212, 217–219, 221–222
Type 2 diabetes 29–30, 56, 58, 62–63, 66–69
European Association for the Study of Diabetes (EASD) 19, 255, 348–349, 406, 438–440, 524, 592, 725–727, 824–825, 831–833
European Carotid Surgery Trialist's Collaborative Group (ECST) 766
European Diabetes Prevention RCT **392**
European driving licences 959–960
European MetaHIT Project 261
European Prospective Investigation into Cancer (EPIC) 747
EVA-3S trial 766
EVAR *see* endovascular aneurysm repair
evidence-based medicine 330, 465–468, 570
EXAMINE trial 542, 726, 737, 741
exchange proteins activated by cAMP (EPAC) *92*
executive function 922–930, 1025–1026, 1029
exenatides 525–529, 538, 542–543
exendin-4 524–529, 1160
exercise
adverse-event risk minimization 398
aerobic 382, 384–400
anaerobic 382–383, 398–400
β-cell function 389–390, 396
blood glucose 398–400
bone density 390, 396
cancers 390, 396
carbohydrates 382, 392, 399–400
cardiovascular disease 382–384, 389, 393–395, 398
children 596, 999–1000, 1004–1010
cultural considerations 992
dietary factors 376, 382–403
education 354–356, 364
energy expenditure 197–199
ethnicity 992, 994
gestational diabetes mellitus 382, 397, 1065
glucose management 382–390, 393–400, 579–588, 592, 596
glycaemic management 382–400
glycated haemoglobin 382, 384–390, 393–397
guidelines 397–398
hyperglycaemia 382–384, 389, 398–400
hypoglycaemia 382–384, 389, 398–400, 579–588, 592, 596
impaired glucose tolerance 382, 390–392
insulin 376, 382–400
metabolic equivalent units 382, 391–392
microvascular complications 396
morbidity 382–384, 389
mortality 382–384, 389–393

exercise (*cont'd*)
obesity 197
older patients 1072–1074, 1078–1082
oral glucose lowering drugs 492–496, 501, 518
patient education 354–356, 364
pregnancy 382, 397, 1065
resistance 382, 384–400
safety 398–399
South Asian populations 992, 994
structured 394–396
travel 970
Type 1 diabetes 382–390, 397–400
Type 2 diabetes 382–384, 389–400
vascular risk factors 389, 395
well-being 390, 396
exocrine pancreas diseases **25**
exogenous genetic material 1144
exogenous insulin administration 438–439
EXSCEL study 415–416, 527, 542, 694, 727, 737
extracellular domain insulin receptors 112–113
extracellular signal-regulated kinases (ERK) 115–116, 685, 827
extracellular vesicles 1142
extrahepatic cancers 820, 823, 828
extra-pancreatic clinical features 281–282, 286–288
eyes 333, 335–336, 350
see also retinopathy
ezetimibe 834

FACET study 690
faecal incontinence 796, 800–802, 807
Falta, Wilhelm 12–13
familial clustering 47–48, 159, 191–194, 197–198
familial partial lipodystrophy 275, 278, 288–291
family-based care groups 354–355, 362–365
family factors
adolescents 1019–1031
behavioural factors 908–919
children 1001–1008, 1012–1015
end-of-life care 1085–1091
psychological reactions 907–915, 918–919, 970, 1005, 1012–1013, 1019–1031
psychosocial aspects 908–919
transition to adulthood 1019–1031
family planning 295–298, 780, 791–792, 1027, 1049
family practitioners 1103–1104
family therapy 908, 911, 916–919
Farmer, Paul 973
farnesoid X receptors (FXR) 261, 267–268
faster insulin aspart (FIASP) 434, 572, 1006–1007, 1046
fasting, cultural aspects 994–996
fasting diets 255–256
fasting glucose
diabetes classification and diagnosis 24
drug-induced diabetes 295, 297–299
genetics 193
glucagon 103, 106–107
monogenic diabetes 275, 280–282
pregnancy 1034, 1050–1060
Type 2 diabetes 56–70
fasting hyperglycaemia 238, 245
fasting insulin 120, 189–190, 193, 264–265, 747, 822, 872, 1150
fasting plasma glucose 1034, 1050–1060
fats, dietary factors 79, 227, 368–375, 718–719, 834–835
fatty acid receptor agonists 266, 718–719, 1156
fatty acids 79, 374, 718–719, 834–835
fatty acid synthesis 79–80
fatty acyl-CoA *239*, 241
feasting 994–995
Federal Crown and Indigenous people 976–977
feet *see* foot disease
female sexual dysfunction 673–674, 780, 788–793
femoro-popliteal bypass 759–760, 764
ferritin tests 326
fetus
see also gestational diabetes mellitus; pregnancy
adverse outcomes 1034–1044
glucokinase MODY 280–281
kidney disease 336–337
malnutrition 57
monogenic causes of diabetes 280–282
obstetric surveillance 1047–1048
physiology 1035–1036
transcription factor MODY 282
FGF *see* fibroblast growth factor
FIASP *see* faster insulin aspart
fibrates 713–721
fibre intake 373
fibrinoid necrosis 748
fibroblast growth factor (FGF) 137–138, 1154, 1162
fibroblasts 1139, 1141
fibrocalculous pancreatic diabetes 319–324
fibroproliferative disorders of soft tissue 853–856
fibrosis, liver 820–835
ficolins 622–624
fiduciary relationship 976–977
FIELD study 718
Finish Diabetes Prevention Study **391**
Finland 41–51, 62–63, 190, 204, 206
FINRISK97 study 264
firmicutes 262–263
First Nations communities in Canada 976–978
first-response management 934, 938
fish 369–370, 374–375, 719
fish oils 291
fitness 382–384, 388, 390, 393, 397
fixed-rate intravenous insulin infusion (FRIII) 565–566
flat, narrow, and in range (FNIR) day 454, 457
fluids
children 999, 1001–1004, 1012–1013
diabetic ketoacidosis 604–606, 1002–1003
gastrointestinal tract 796, 806–807
hyperosmolar hyperglycaemic syndrome 602, 608–610
fluorescein angiography 635–636
fluoroquinolone-associated dysglycaemia 295, 300–301
fluoxetine 151, 938–939, 947
FNIR *see* flat, narrow, and in range day
focal/multifocal neuropathies 655–663, 670
folic acid 368, 376
food
amylin 529–530
body weight 142–152, 197–199
GLP-1 523
obesity 197–199
snacking 372, 399, 568–569, 1006–1012
travel 970
foot disease 771–779
aetiopathogenesis 772–774
amputations 771–779
black toe 330, 336
care aims 350
Charcot neuroarthropathy 657, 771, 778
clinical presentation 336
deformities 774–775
dressings 776–777
economic aspects 771
elevated pressure 774
epidemiology 771
footwear 775
healing 771–778
historical perspectives **4**, 8–9
hospitalization 771–779
hyperbaric oxygen 778
infections 771–778, 878–893
in-hospital care 575
lesions 772–774
lower-limb amputations 771–773
management 771–778
mortality 771
negative pressure 778
neuropathy 655–664, 667–677, 771–778
offloading 776
osteomyelitis 777
patient education 771, 774–775
peripheral arterial disease 771, 773–775
plantar callus 774
prevention strategies 774–778
risk factors 771–778
screening 772–773
self-care 771, 774–775
sensorimotor polyneuropathy 655–664, 667–670
sensory protection 772
skin temperature 775
surgical management 771–779
ulceration 655–663, 667–671, 771–778, 1102
foot pressures 774
footwear 775
forkhead box O subfamily (FoxO) 117, 122–123
Fournier gangrene 878, 892–893
fractures 793, 859–863
fragility fractures 793, 859–863
frailty in older patients 1072–1083
Framingham Heart Study 713, 732–733, 745
France 44, 62–63, 1072
frank diabetes 323–324
Frank, E 16–17
free diet movement 17
free fatty acids 507–508, 603–608, 715–716, 826–828, 1035–1036
FreeStyle Libre 445, 447

frequency-modulated electromagnetic neural stimulation (FREMS) 668
Freychet, Pierre 15
FRIII *see* fixed-rate intravenous insulin infusion
frozen shoulder 854–855
fructosamine 408
fructose 373
FTO genes 157, 190, 193
fulminant type 1 diabetes 216–217
fundus photography 629, 631, 634–635
fungal infections 336, 838–839, 845–848, 878, 881–882, 890–891
FXR *see* farnesoid X receptors

GAD *see* generalized anxiety disorder; glutamic acid decarboxylases
GADA *see* glutamic acid decarboxylase autoantibodies
gallbladder dysfunction 671
gallstone disease 556
gamma-aminobutyric acid (GABA) 666
gangrene 878, 892–893
gastric banding 832
gastric bypass 250, 255, 258
gastric emptying 529–530, 796–807
gastric inhibitory polypeptides (GIP) 144, 231, 535–547, 1156–1160
gastric outlet obstruction 796, 803
gastrointestinal peptides 1158–1159
gastrointestinal tract *78*, 80–82
  abdominal pain 605, 796, 801–804
  abscesses 890–891
  animal studies 798–799
  autonomic dysfunction 797–798, 802–803, 806
  bacterial overgrowth 796, 800–801, 806–807
  body weight 142–144, 197–199
  clinical presentation 802–804
  complications 796–809
  constipation 796, 800–808
  diagnostics 804–806
  diarrhoea 672–673, 796, 800–807
  digestion 797–802, 805–807
  dyspepsia 796, 800, 802–807
  dysphagia 796, 802
  epidemiology 796–797
  faecal incontinence 796, 800–802, 807
  gastric emptying 529–530, 796–807
  gastroparesis 671–672, 796, 800, 802–807
  GLP-1 523
  GLP-RA 801
  glucose homeostasis 129, 131, 135, 139
  glucose metabolism *78*, 80–82
  glycaemic management 796–798
  heartburn 796, 802
  hydration 796, 806–807
  hyperglycaemia 796–798
  infections 890–891
  insulin secretion/islet function 84, 89, 93–96
  irritable bowel syndrome 796–797
  macrophage modulation 799–800
  management 797–809
  manifestations of 796–809
  microbiome 81, 261–269
  motor functions 797–798
  nausea 602, 605, 796, 802–807
  nephropathy 797, 802
  neuropathy 671–673, 797–806
  nutrition 796–797, 802, 806–807
  obesity genetics 197–199
  oesophageal dysmotility 671, 802
  opioids 801
  oxidative stress 799–800
  pathophysiology 797–802
  quality of life 796–797, 801, 807
  retinopathy 797, 800, 802
  sensorimotor dysfunction 796, 802
  symptomatic measures 796, 801–802, 805–807
  Type 1 diabetes 796–798, 801–802, 807
  Type 2 diabetes 796–797, 800–803, 807
  vomiting 605, 796, 802–807
gastroparesis 671–672, 796, 800–807
GCGR *see* glucagon receptors
GCK *see* glucose-sensing enzyme glucokinase
GDM *see* gestational diabetes mellitus
gender-related incidence
  NAFLD 820, 825, 828, 831
  Type 1 diabetes 41–43, 204
generalized anxiety disorder (GAD) 939–942
generalized granuloma annulare 838, 842–843, 847–848
general practitioners 1103–1104
general ward inpatient treatments 561–562
generic end-of-life guidance 1085, 1087–1088
generic quality of life 912–913
gene therapy 1144–1153
  see also genetics
  adipose tissue 1144, 1149–1150
  animal models 1144–1151
  β-cells 1147–1148
  ectopic insulin production 1146
  efficacy 1144, 1146–1150
  energy expenditure 1144, 1149–1150
  glucose disposal enhancement 1147
  glucose tolerance 1144, 1147–1150
  immune modulation 1148–1149
  inflammation 1144, 1146–1150
  insulin 1144–1151
  islet cell transplantation 1145–1146
  non-viral vectors 1144, 1148–1150
  obesity 1150
  safety 1144–1150
  surrogate cell reprogramming 1147–1148
  thermogenesis 1149–1150
  Type 1 diabetes 1144–1149
  Type 2 diabetes 1149–1150
  viral vectors 1144–1151
genetics
  Albright hereditary osteodystrophy 198
  autoimmune Type 1 diabetes 207–210
  biomarkers/precision medicine 414–426
  body weight 142, 148–152, 197–201
  children 197–201, 1001–1002
  complex phenotypes 157, 160, 192
  developmental delay 198–200
  DNA methylation 157, 191–194
  function assignment 192–193
  gene-editing techniques 488
  gene–environment interactions 157, 160, 190–191
  gene–gene interactions 157, 160, 190–191
  gene methylation 149
  genetic engineering 1145–1146
  genetic loci 160–166, 168–189, **189**
  genetic polymorphisms 615, 619, 623–624, 1125–1126
  genetic testing 278–281, 285–286
  gene transcription 101
  haemochromatosis 324–325
  heritability 159–160, 167, 191–192, 197–202, 324–325
  histone modifications 157, 192–194
  hypothalamus 197–201
  islet autoimmunity 207–210
  latent autoimmune diabetes 157–159, 194
  LincRNAs 192
  linkage studies 157, 160, 167, 190
  Mendelian disorders 197–198
  mental disorders 933, 937–938, 949
  microRNAs 157, 160, 192
  mitochondrial mutations 221–222
  MODY 157–160, 278–281
  monogenic diabetes 157–160, 275–291
  NAFLD 820, 825–828
  nephropathy 644
  non-coding RNAs 192
  obesity 142, 148–152, 197–202, 250–254, 1150
  paraganglioma 312
  parent-of-origin effects 157, 160, 191–192
  pathogenesis 157–202
  phaeochromocytoma 312
  Prader-Willi syndrome 198
  predisposition 228–230
  protective variants 190, **191**
  psychosocial aspects 933, 937–938, 949
  psychotic disorders 949
  rare variants 167, 190, 197, 200–201
  sequencing 157–160, 167, 223
  single-nucleotide polymorphisms 157, 160–167, 189–194
  Type 1 diabetes 45–52, 157–166, 190–194, 207–210, 221–222, 1125–1126, 1144–1149
  Type 2 diabetes 56–58, 157–194, 228–230, 250–254, 1149–1150, 1164–1165
genitourinary infections *78*, 791, 878, 892
genome-wide association studies (GWAS)
  genetics pathogenesis 157, 160–194
  insulin resistance 243
  NAFLD 825–826
  obesity 197, 201
  Type 2 diabetes 157, 160–194, 228–230, 243
genotype-based treatments 193
geographic variation
  see also individual countries
  African Americans 978–979
  obesity 250
  Type 1 diabetes 42–52
  Type 2 diabetes 55–71
Gepts, Willy 13
geriatric assessments 1072, 1074–1075, *1081*, 1082
geriatric syndromes 1072–1078, 1082
Germany 36–37, 44–47, 886, 917–918
gestational diabetes mellitus (GDM)
  breastfeeding 1065
  cancers 871

gestational diabetes mellitus (GDM) (*cont'd*)
carbohydrates 1050
classification and diagnosis 23, 26–27
clinical presentation 330, 336–337
diagnosis 1049–1054
dietary factors 1058, 1065–1066
disease entity 1054–1055
exercise 382, 397, 1065
future directions 1066
global burden **29**, 31
hyperglycaemia 1050–1054
lifestyle factors 1058, 1063–1066
long-term outcomes 1061–1063
management 397, 1058–1066
obesity 1060–1061
pharmacology 1058–1059, 1065
physical activity 382, 397
postnatal aspects 1063–1066
postpartum management 1059–1060
pregnancy 1034–1036, 1041–1046, 1049–1066
prevention 397
risk factors 1054–1055
screening 26–27
sulfonylureas, pregnancy 1059
GFR *see* glomerular filtration rate
ghrelin 93, 143–144
gingivitis 810–816, 818
GIP *see* gastric inhibitory polypeptide; glucose-dependent insulinotropic peptides
GIPR function assignment 192–193
glargine 726
glial cell types 133
glibenclamide 492, 494, 496, 501–504
glicentin-related pancreatic polypeptide (GRPP) 101, 521–522
gliclazide 492, 496, 501–504
gliflozins 17, 534–536, 539–548
glimepiride 492, 496, 501–504
glipizide 492, 494, 496, 501–504, 850
gliptins *see* dipeptidyl peptidase-4 inhibitors
glitazones 17, 535, 537–542, 546–547
global burden of diabetes 28–40
cancer 34
cardiovascular disease 32–34
cognitive disabilities 35
complications 32–35
costs of diabetes 35–37
diabetic ketoacidosis 33
disabilities 34–37
economic costs of diabetes 35–37
end-stage renal disease 33–34
gestational diabetes mellitus **29**, 31
infections 34–35
lower-extremity amputations 32–33
mental health disorders 34–35
mortality 31–37
neuropathy 33
physical disabilities 34–35
prevalence 29–32
retinopathy 33
socioeconomic costs of diabetes 36–37
Type 1 diabetes 29
Type 2 diabetes 29–32
global LMIC care models 1107–1118
global-related obesity incidence 250
globin insulin 16
glomerular filtration rate (GFR) 640–651
GLP-1 *see* glucagon-like peptide 1
GLP-1R *see* glucagon-like peptide 1 receptors
GLP-1RA *see* glucagon-like peptide 1 receptor agonists
GLP-2 *see* glucagon-like peptide 2
glucagon
action 106–107, 1160
amino acids 99–101, 104–107
central nervous system 100, 105
children 1011
drug development 99, 107–108
endocrine 99–107
energy balance 99, 103–105, *107*, 108
gene transcription 101
glucose metabolism 79, 102–104
G-proteins 99, 101–105
hepatic–α-cell axis 104–105
hepatocytes 99, 103, *107*
hypersecreting endocrine disorders 304–305, 309, 313–315
hypoglycaemia 579–596
insulin secretion/islet function 93–95, 105
intra-islet signalling 99, 101, 105
islet α-cells 99–108
islet β-cells 99–107
islet regulation 99–110
lipid metabolism 99, 102–107
liver 102–105
metabolic regulation 99–110
peptide processing 101
pharmacology 99, 107–108
proglucagon gene transcription 101
secretion 106–107, 523, 1160
systemic glycaemia regulation 99–110
glucagon-like peptide 1 (GLP-1) 492–498, 504, 508–511, 514–518
α-cell production 105–106
anti-diabetic effects 522–524
appetite-regulation 523
β-cell function 231–232
body weight 143–144
brain control 129, 138–139
cardiovascular system 523
food 523
gastrointestinal tract 523
glucagon secretion 102, 523
glucose homeostasis 129, 138–139
historical perspectives 17, 521–523
incretin effect 521–522
insulin secretion 94–95
metabolism 79, 81, 94–95, 522–523
microbiome 266–268
neuroprotective effects 524
obesity 250, 256–258
pancreatic insulin 523
parenteral therapies 520–530
physiology 522–524
proglucagon distribution 522–523
renal function 523–524
stroke 749
Type 2 diabetes 266–268, 520–530
glucagon-like peptide 1 receptor agonists (GLP-1RA) 493–498, 508–510, 514
adolescents 1026–1027
adverse-effects 520, 525–529
β-cell dysfunction 232
biomarkers/precision medicine 416, 420–421
body weight 520–530
cardiovascular outcome trials 520, 523–530
care aims 350
gastrointestinal tract 801
glucose homeostasis 138–139
heart failure 741–742
history of diabetes mellitus 3, 15–17
hypersecreting endocrine disorders 309–310, 317
hypoglycaemia 528
immunogenicity 528–529
insulin secretion 232
insulin therapy 431, 438–441
interactions, safety 529
ischaemic heart disease 724–727, *729*
islet and metabolic regulation 95–96, 99, 107
microvascular complications 615–616, 626
monogenic diabetes 282, 291
NAFLD 820, 825, 832–834
nephropathy 648
obesity 200, 250, 256–258
pancreatic adverse events 528
parenteral therapies 520–521, 523–530
pathogenesis 615–616, 626
pharmacokinetics **524**
safety 528–529
thyroid adverse events 528
transition to adulthood 1026
Type 2 diabetes 534, 538–548, 1154–1160, 1163–1164
glucagon-like peptide 1 receptors (GLP-1R)
biomarkers/precision medicine 420
body weight 144
glucose homeostasis central control 139
history of diabetes mellitus 15
islet function/insulin secretion 95
islet and metabolic regulation 102, 105–108
parenteral therapies 520–526, 530
glucagon-like peptide 2 (GLP-2) 101, 314, 521–522
glucagonomas 305, 313–315
glucagon receptors (GCGR) 102–108, 227
glucocorticoid inhibitors 1154
glucocorticoids
drug-induced diabetes 295–296
glucose metabolism 82
hypersecreting endocrine disorders 304, 308–313
in-hospital treatments 574
Type 2 diabetes 1154, 1162
glucocorticosteroids 1091
glucoganoma syndrome 847
glucokinase activators 1156
glucokinase genes 275–286
glucokinase MODY 279–281
gluconeogenic pathway enhancement 103
glucoregulatory neurocircuits 128–131, 134–135
glucose
see also blood glucose; glucose. . .; glycaemic management
alarms 451
ambulatory profiles 452–457

cardiovascular disease 713–714
complications 682–696, 713, 717, 718
counter-regulation 107, 313, 579–588, 591
deficiency responses 135–137
dietary factors 382, 390–392
disposal enhancement 1147
exercise 382–390, 393–400, 579–588, 592, 596
frequency of measurements 445–446
future insulin therapy, s 441–442
glucosuria 492–493, 511–514, 547, 726, 1162–1164
high *see* hyperglycaemia
homeostasis 128–141
  autonomic control 129–130
  β-cell dysfunction 128, 130, 136–137
  biologically defended levels 128, 135–139
  body temperature 134–135
  central control 128–141
  circadian control 130
  drug-induced diabetes 295, 298–301
  evolutionary considerations 128
  gastrointestinal tract 129, 131, 135, 139
  hypersecreting endocrine disorders 304, 308, 311
  insulin secretion 128–132, 135–139
  insulin signalling 123
  islets 128–139
  liver 129–134, 138
  metformin 139
  neurons 128–139
  obesity 128, 131–137
  pancreas 128–139, *134*, 139
  parasympathetic nervous system 129–130
  skeletal muscle 123
  sympathetic nervous system 129–130
  thermoregulation 134–135
  Type 2 diabetes 128, 131–139
index 452
in-hospital treatments 559, 561–562
insulin novel treatments 444–468
intolerance 304, 315–316
ischaemic heart disease 724–726
lactate shuttle hypothesis 133–134
low *see* hypoglycaemia
management
  complications 682–696, 713, 717, 718
  exercise 382–390, 393–400, 579–588, 592, 596
  historical perspectives 17–18
  nephropathy 640–641, 644–652
  novel technologies 444–468
metabolism 77–96
  brain 77–78, 81–82
  carbohydrates 78–81
  gastrointestinal tract *78*, 80–82
  hormones 77–82
  insulin 77–96
  islet function 77–81, 84–96
  kidney *78*, 81–82
  liver *78*, 79–80
  normal physiology 77–96
  pancreatic islets 77–78, 81
  tissues 77–82
  Type 2 diabetes 1154–1157
novel technologies 444–468
  physical activity 382, 390–392
  post-exercise 399–400
  quality 445–446
  renal thresholds 330–331
  tablets 349, 594, 1011
  tolerance
    acromegaly 305–308
    Cushing syndrome 308–312
    diabetes classification and diagnosis 23–24
    gene therapy 1144, 1147–1150
    hormone replacement therapy 793
    hypersecreting endocrine disorders 304–317
    paraganglioma 312–313
    phaeochromocytoma 312–313
    physical activity 382, 390–392
    Type 2 diabetes 55–71
  toxicity 240–241
  transport 117–118, 132–133, 225–228, 238–247
  travel 968–969
  Type 1 diabetes 398–400
  urine measurements 410
  variability 452–453
glucose-dependent insulinotropic peptides (GIP)
  function assignment 192–193
  glucagon release 102
  glucose metabolism 79, 81
  insulin secretion 95
  obesity 250, 256–257
  parenteral therapies 521–522, 529–530
  Type 2 diabetes 534–540, 543, 546–547
glucose–fatty acid cycle 241, 306, 496
glucose-responsive smart insulins 459, 470, 1154, 1164
glucose-sensing enzyme glucokinase (GCK) 275–281
glucose transporter 2 (GLUT2) 225
glucose transporters (GLUT) 117–118, 132–133, 225
α-glucosidase inhibitors 496–498, 503–504, 514–516, 534, 537, 873
glucosuria 492–493, 511–514, 547, 726, 1162–1164
glucotoxicity 216–218, 230–232, 683–684
glues, skin reactions 838, 850
GLUT *see* glucose transporters
glutamic acid decarboxylase 65 (GAD65) 25, 203–204, 212
glutamic acid decarboxylase autoantibodies (GADA) 203–213, 218
glutamic acid decarboxylases (GAD) 25–26, 203–204, 212, 1126–1127, 1133–1134
glyburide 492, 494, 496, 501–504
glycaemic index (GI) 80, 368–373, 1008
glycaemic management
  adolescents 1020–1029
  alcohol 963–964
  assessment importance 437–438
  behavioural factors 907–918
  biologically defended levels 128, 135–139
  biomarkers/precision medicine 414–420, 425–426
  cardiovascular disease 713–716
  care aims 346–352
  children 999–1000, 1003–1015
  cognitive function 922–926
  depression 936–939
  dietary factors 368–376
  education 437–438
  end-of-life care 1085–1093
  gastrointestinal tract 796–798
  glucose homeostasis 128–139
  historical perspectives 17
  infections 879–894
  in-hospital treatments 559–575
  insulin novel delivery technologies 459–470
  islet cell transplantation 473–488
  microbiome 261, 264–267
  monitoring diabetes 404–420, 444–457
  obesity 250–258
  older patients 1072–1082
  oral glucose lowering drugs 492–518
  physical activity 382–400
  pregnancy **25**, 27, 1034–1066
  psychosocial aspects 907–918, 922–926
  stroke 745, 747–752
  transition to adulthood 1020–1029
  Type 1 diabetes 52, 384–389
  Type 2 diabetes 393–395, 540–541, 1154–1165
  whole pancreas transplantation 473–488
glycaemic memory 616–618, 683–684
glycaemic traits **189**
glycated haemoglobin (Hb_{A1c})
  adolescents 1020–1031
  advantages and disadvantages **24**
  assays 406–407
  biomarkers/precision medicine 415, 417–422, 425
  children 999–1001, 1004–1007, 1011–1016
  diabetes classification and diagnosis 24
  discovery 17
  drug-induced diabetes 295, 297–299
  end-of-life care 1085, 1088, *1092*
  gestational diabetes mellitus 27
  global burden of diabetes 32
  insulin novel technologies 459–468
  monitoring diabetes 404–412, 444–445, 449–452
  NAFLD 820, 822, 825, 829
  patient education 354, 361, 364
  physical activity 382, 384–390, 393–397
  point-of-care 407
  pregnancy 1034–1041, 1044–1047, 1053–1060
  stroke 745, 747–749
  transition to adulthood 1020–1031
  Type 1 diabetes 404–405, 408–412
  Type 2 diabetes 26, 393–395, 406, 540–541
glycogenic theory 6–7
glycogen storage 78–80, 945, 947
glycolysis 24, 80, 409
Goeddel, David 16
Gold Standards Framework 1086–1088
golimumab 1132
gout 857–858
governance aspects 1110, 1117–1118
G-protein–coupled bile acid receptors (TGR5) 261, 267–268
G-protein–coupled receptors (GPRs) 266–267
G-proteins 99, 101–105, 124

GPRS *see* G-protein–coupled receptors
grafts 473–488
granuloma annulare 838, 842–843, 847–848
Graves' disease 316
Greece 63
Griesinger, Wilhelm 8
group-based patient education 354–365
group therapy 907, 918–919
growth factors
  pathogenesis 615, 619, 621–622, 625
  retinopathy 632, 637–638
growth hormones 82, 143–144, 304–312, 316–317
GRPP *see* glicentin-related pancreatic polypeptide
gustatory sweating 674
gut-derived factors 94–96
gut hormones 145–146
gut microbiome 81, 145, 261–271
GWAS *see* genome-wide association studies
gynaecological trauma 789

HAART *see* highly active antiretroviral therapy
Habener, Joel 17
HADS *see* Hospital Anxiety and Depression Scale
haemochromatosis 319–320, 324–326
haemodynamic factors 615, 619–622, 681–682, 686–687
haemoglobin (Hb_{A1c}) *see* glycated haemoglobin
Haemophilus infections 892
haemorrhages 629–637
Haemorrhagic Stroke Project 747
Hagedorn, Hans Christian 16
HAIR-AN syndrome 289
hands
  bone and joint disorders 853–858
  endocrine disorders 305
  neuropathy 656–657, 663–664, 670
  skin 840–841, 846–847
haplogenotypes 203, 205–213
HAPMAP 167
HAPO *see* Hyperglycemia and Adverse Pregnancy Outcomes
harm from in-hospital hyperglycaemia 560–561
Harmony Outcomes trial 543
Hb_{A1c} *see* glycated haemoglobin
HBV *see* hepatitis B virus (HBV)
HDL *see* high density lipoproteins (HDL)
head/neck infections 218, 313, 884–885
Health Belief Model 358
healthcare
  burden 68–71
  integrated 1097–1099, 1102–1105, 1113–1114, **1117**
  LMIC models 1108–1118
  patient involvement 352, 354–365
  professionals 356–365, 1085–1093
  social determinants of diabetes 979–983
  teams 343–365, 817–818, 933, 938–939, 946–947
health inequalities 991
health-related quality of life 912–913
health social determinants of diabetes 974–982
health workers 1105
heartburn 796, 802
heart disease 793
Heart and Estrogen/Progestin Replacement Therapy Study (HERS) 298
heart failure 724–744
  anti-diabetic oral agents 741–742
  β-blockers 732, 739–741
  cardiac resynchronization 740–741
  chronic kidney disease 734
  comorbidity 732–740
  dyslipidaemia 733–734
  epidemiology 732–734
  hospitalization 732–742
  hyperglycaemia 732–734
  hypertension 733
  ICDs 740
  left ventricular ejection fraction 732, 740–742
  lifestyle factors 735–736
  management 732–742
  mineralocorticoid receptor antagonists 732, 739–741
  mortality 732, 738–741
  myocardial infarction 732–742
  obesity 734
  pathophysiology 734
  prevention strategies 735–737
  RAS inhibitors 732, 734, 738–740
  reduced ejection fraction therapies 738–741
  risk factors 733–737
  SGLT-2 inhibitors 732, 737–741
  stem cell therapy 1140–1141
  subclinical abnormalities 733
  Type 2 diabetes 534–538
Heart Protection Study 716, 718, 1077
hemochromatosis 286, 326
hepatic acetyl-coenzyme A content 238, 245
hepatic–α-cell axis 104–105
hepatic glucagon signalling 99, 103–104
hepatic gluconeogenesis 238–239, 245–247
hepatic insulin receptors 122–123
hepatic insulin resistance 238, 242–247
hepatic protein metabolism 99
hepatitis B virus (HBV) 883–884
hepatitis C infections 878, 882–883
hepatocellular ATP 243
hepatocellular carcinomas 820, 823–835
hepatocellular injury 820–823, 826–828
hepatocytes 99, 103, *107*
hepatoselectivity 441–442
hereditary haemochromatosis 319–320, 324–326
heritability
  basal metabolic rate 197–198, 201
  body fat distribution 197–199
  energy expenditure 197–199
  familial clustering 159, 191–194, 197–198
  monogenic diabetes 275–291
  obesity 197–202, 250, 252
  twin studies 197–198
  Types 1 and 2 diabetes 157–160, 167, 191–194
hernias 556
herpes simplex vectors (HSV) 1146
HERS *see* Heart and Estrogen/Progestin Replacement Therapy Study
hESC *see* human embryonic stem cells
heterogeneity 158–160, 194
heterogeneous diseases 1133–1134
heterologous regulation 118–121
heterozygous rare gene variants 200–201
Heyl, Albert **4**
HGI *see* high glucose index
HHEX genes 157, 167
HHS *see* hyperosmolar hyperglycaemic syndrome
HIC *see* high-income countries
high density lipoproteins (HDL) 281–282, 290–291, 424–425, 701–702, 713–721, 727–730
  clinical trials 683–685
  insulin resistance 246–247
high glucose index (HGI) 452
high-income countries (HIC) 29, 32–36, 1108–1116
highly active antiretroviral therapy (HAART) 60
Himsworth, Harold 12–13
Hispanic populations 30, 46, 61–62, 337, 745–746, 868, 975
histone modifications 157, 192–194
histopathology 641–643
historical perspectives 3–21
  17th and 18th centuries 4–6
  19th century 6–8, 22
  20th century 8–20
  amylin 529
  ancient times 4, 22
  care delivery 18–20
  causation aspects 12–13
  chronic complications 13–14
  clinical presentation **4**, 8
  complication aspects 13–14, **16**, 18
  diabetes classification and diagnosis 22
  diabetic ketoacidosis **4**, 18–19
  GLP-1 521–523
  insulin therapy **15**, 16–17, 431–432
  islet cell transplantation 476–477
  management 15–20
  milestones **4**, **6**, 14
  natural history 12–13
  physiology 14–15
  pregnancy 18–20
  whole pancreas transplantation 474
HIV *see* human immunodeficiency virus
HLA *see* human leucocyte antigens
HMG CoA (3-hydroxy-3-methylglutaryl coenzyme A) *see* statins
HNF1A/HNF4A transcription factor genes 275–288
Hodgkin, Dorothy, nee Crowfoot 14–15
Hofmeister's oral glucose tolerance test 23–24, 27, 61
holistic care approaches 343, 345–346, 575, 1082, 1085–1093
Holler, Jacob 18
Holst, Jens Juel 17
home blood pressure 700, 704
homeostasis model assessment B (HOMA-B) 227
homeostasis model assessment of insulin resistance (HOMA-IR) 253
HONK (hyperglycaemic hyperosmolar non-ketotic coma) *see* hyperosmolar hyperglycaemic syndrome

HOPE trial 749
hormonal contraception 792
hormone replacement therapy (HRT) 295, 298, 780, 791–793
hormones
  appetite-regulation 142–146, 149–151
  body weight 142–146, 149–151
  glucose metabolism 77–82
  growth 82, 143–144, 304–312, 316–317
  insulin secretion/islet function 84–89, 92–96
  oral glucose lowering drugs 492–493, 496, 503–504, 508–515
  sexual dysfunction 782, 791
hosiery 775
Hospital Anxiety and Depression Scale (HADS) 938, 940, 942
hospitals
  see also in-hospital treatments
  admission 571–573, 575
  discharge 573–575
  foot disease 771–779
  heart failure 732–742
  in-patient surgical care 35–36, 559–578, 945–947, 1004, 1102
host factors, infections 880–882
host immune development 268–269
HOT *see* Hypertension Optimal Treatment
hot climates 970
housing aspects 978–979
HRT *see* hormone replacement therapy
HSV *see* herpes simplex vectors
human embryonic stem cells (hESC) 475, 485, 488, 1137
human genome 111
human immunodeficiency virus (HIV) 151, 299–300, 878, 882–883, 886–887, 1108–1110, 1113–1117
human insulin gene sequences 15
humanitarian emergencies 1111
human leucocyte antigens (HLA) 25, 41, 48, 205–213, 1125–1126
human resources 1109, 1116–1118
humoral immunity 212, 878
Hungary *44*, 1113
hybrid closed loop systems 444–445, 454–457, 579, 593, 597, 1007, 1034–1035
hybrid peptides 1159–1160
hydration 602, 604–610, 796, 806–807, 1002–1003
3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors *see* statins
hydroxysteroid dehydrogenase 1 inhibitors 1162
hygiene 261, 268
hygiene hypothesis 49–50, 882
hyperaldosteronism 316
hyperandrogenism 304, 314, 316–317
hyperbaric oxygen 778
hypercholesterolemia 414, 423–425
hypercoagulability 696, 745
hyperfiltration 644
hyperglycaemia
  see also hyperosmolar hyperglycaemic syndrome
  acute illness 560
  adolescents 1020–1025, 1028–1029
  alcohol 964
  β-cell function 230–232
  biomarkers/precision medicine 414, 417–419
  cancers 867, 871–872, 875–876
  carbohydrates 372
  cardiovascular disease 713, 715–718
  care aims 343, 346–351
  cell response 616
  children 999–1009, 1012–1013
  clinical presentation 330–334
  clinical trials 682
  cognitive function 922–926
  complications 615–626, 682–696, 713, 715–718
  dementia 1080
  depression 936–937
  diabetic ketoacidosis 604
  dietary factors 368–376
  drug-induced diabetes 295–302
  gastrointestinal tract 796–798
  gestational diabetes mellitus 1050–1054
  glycaemic memory 616–618, 683–684
  heart failure 732–734
  historical perspectives 4–5, 7, 12
  hypersecreting endocrine disorders 304–309, 313–315
  induced mitochondrial superoxides 615, 617
  infections 879–894
  in-hospital treatments 559–566, 570–575
  insulin resistance 238, 240–247, 684
  insulin therapy 459–463, 468–469
  legacy effect 616–618
  management 347–348, 492–518, 559–566, 570–575
  medication factors 347–348
  nephropathy 643
  novel monitoring technologies 444–446, 449–454, 457
  older patients 1074–1081
  oral glucose lowering drugs 348, 492–518
  pancreatic diseases 319–320, 327
  pathogenesis 615–626, 682–696
  pathophysiology 560
  physical activity 382–384, 389, 398–400
  pregnancy **25**, 27, 1034–1042, 1045–1063
  psychosocial aspects 922–926
  recognition in older patients 1078–1080
  stroke 745, 747–753
  surgical management 559–566, 570–575
  susceptibility determinants 618–619
  symptoms 347–348
  transition to adulthood 1020–1025, 1028–1029
  Type 2 diabetes 71, 230–232, 238, 240–247, 534, 537–541, 548
hyperglycaemic hyperosmolar non-ketotic coma (HONK) *see* hyperosmolar hyperglycaemic syndrome
Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study 336, 1051–1056, 1060–1063
hyperinsulinaemia
  cancers 867, 871–872, 875–876
  hypersecreting endocrine disorders 316–317
  insulin resistance 288–290
  management 579–588, 594–597
hyperinsulinaemic–euglycaemic clamp test 238
hyperlipidaemia **4**, 230–231, 655–656, 670, 673, 745–749
hyperosmolar hyperglycaemic syndrome (HHS) 602–604, 608–610
  adolescents 1028
  care aims 351
  children 1004
  clinical presentation 334, 608–610
  diagnosis 608–610
  electrolytes 602, 609–610
  end-of-life care 1085–1086
  fluid therapy 602, 608–610
  hypovolaemia 602, 608–610
  infections 602, 608–610
  insulin therapy 602, 608–610
  management 602–604, 608–610
  pathogenesis **603**
  pathophysiology 608
  precipitating factors 608
  prevention strategies 609
  stress hormones 602, 608–610
  transition to adulthood 1028
  Type 2 diabetes 602, 608–610
hyperparathyroidism 316
hyperplasia 304, 316
hypersecreting endocrine disorders 304–318
  acromegaly 304–308
  Addison disease 317
  adenomas 304–316
  aldosterone hormones 304, 316
  androgen steroids 304, 314, 316–317
  catecholamines 304, 312–314
  clinical presentation 304–305
  Cushing syndrome 304, 308–312
  diagnosis 306–317
  glucagon 304–305, 309, 313–315
  glucagonomas 305, 313–315
  glucocorticoids 304, 308–313
  glucose tolerance 304–317
  Graves' disease 316
  growth hormones 304–312, 316–317
  hyperaldosteronism 316
  hyperglycaemia 304–309, 313–315
  hyperinsulinaemia 316–317
  hyperparathyroidism 316
  hyperplasia 304, 316
  hyperthyroidism 304, 315–316
  hypoparathyroidism 304, 313, 316–317
  insulin resistance 304–309, 315–317
  management 306–313
  pancreatic islet cell adenomas 304–315
  paraganglioma 304, 312–314
  parathyroid hormones 304, 313, 316–317
  phaeochromocytoma 312–313
  polycystic ovarian syndrome 304, 314, 316–317
  somatostatin 304–315
  somatostatinomas 305, 313–315
  thyroid hormones 304, 315–316
  thyrotoxicosis 304, 315–316
  tumours 304–305, 312–317
  vasoactive intestinal peptides 304, 312, 315
  weight loss 313–314, 316

hypertension 694–695, 700–712
see also anti-hypertensive agents
ACE inhibitors 707–708
α1-adrenoceptor antagonists 708
angiotensin II type 1 receptor blockers 708
β-adrenergic blocking agents 706–708
biomarkers/precision medicine 414
blood pressure 700–711
calcium channel antagonists 707
cardiovascular disease 700–710, 713–716
causation aspects 701–703
children 1015
clinical outcome assessments 709–711
combination therapies 700, 703–704, 706–709
diagnosis 704–705
direct renin inhibitors 708
diuretics 706
ethnicity 709
heart failure 733
impacts of 702–703
investigations 705
ischaemic heart disease 724, 729
management 700, 703–711
metabolic syndrome 701–702
nephropathy 700–704, 707–710
neuropathy 655–656, 670–674
non pharmalogical treatments 706
older patients 1075–1077
pregnancy 1041–1043, 1045–1046
prevalence 700–701
RAAS 700, 702, 707–709
retinopathy 700–703, 709–710
screening 703–704
sexual dysfunction 782, 789
stroke 745–753
Type 1 diabetes 700–702, 705–708
Type 2 diabetes 700–711
Hypertension Optimal Treatment (HOT) 695
hyperthyroidism 304, 315–316
hypertriglyceridaemia 728–729
Hypoboxes 570
HypoCOMPaSS trial 593, 918
hypoglycaemia 579–601
absolute insulin excess 579–582, 588, 593–596
adolescents 1020–1029
age-related incidence 579–580, 590, 594–597
alcohol 579–580, 588, 592–596, 963–964
autonomic neuropathy 580–584
avoidance strategies 566–570
awareness aspects 579–597, 1011
behavioural factors 907–913, 917–918
β-cells 579–588, 593
brain 135–137, 579–588
carbohydrates 579–582, 588, 594–596
cardiovascular disease 590–591
catecholamines 583–584, 595–596
causation aspects 568
children 579–580, 590, 594–597, 999, 1003–1016
classification 591–592
clinical definitions 591–592
clinical management 579–582, 589–592
cognitive function 924–926, 930–931
compromised defences 588–589
consequences 595–596
counter-regulation 99, 579–588
definitions 591, 595
depression 936–939
driving 957–958
education 579, 587–588, 592–596
end-of-life care 1085–1093
epinephrine 579–588
exercise 579–588, 592, 596
frequency 568, 589–590
GLP 1RA 528
glucagon management 579–596
glucose homeostasis 135–137
historical perspectives **15**, 16–17
hybrid closed loop systems 579, 593, 597
hyperinsulinaemia 579–588, 594–597
impacts 590, 595–596
impaired awareness aspects 579–597
in-hospital treatments 559–572, 574–575
insulin 459–470, 579–597
islet cell transplantation 473–484, 488
management 579–601, 1011
manifestation 580
mortality 568, 596
neural activation 579–588
neurological sequelae 596
novel monitoring technologies 444–457
obesity 250, 253–255, 258
older patients 1072–1082
oral lowering agents **15**, 16–17, 492–494, 497–498, 500–518
pathophysiology 579, 582–589
physical activity 382–384, 389, 398–400
physiological effects 595–596
pregnancy 1034, 1037–1051, 1056, 1059–1061
prevalence 595
prevention strategies 592–594, 1009–1012
psychosocial aspects 907–913, 917–918, 924–926, 930–931
recreational drug use 967
relative insulin excess 579–582, 588, 593–596
risk factors 579–597
signs and symptoms 595, 1011
sleep 579, 584–589, 594–597
sympathoadrenal activation 579–588
technology 579, 588, 592–597
therapeutic hyperinsulinaemia 579, 582–588
transition to adulthood 1020–1029
Type 1 diabetes 579–587
Type 2 diabetes 135–137, 579, 582–597
whole pancreas transplantation 473–484, 488
Hypoglycaemia Study Group 589
hypogonadism 147–148, 198–199, 253, 325–326, 781–786
hypokalaemia 298, 315–316, 607, 945, 1003–1004
hypoparathyroidism 304, 313, 316–317
hypopituitarism 308, 325
hyposalivation 810, 816–818
HYPO score 476, 479
hypothalamus 144, 147–148, 197–201
hypothyroidism 316–317, 325, 1016
hypovolaemia 602, 608–610
IA-2 *see* islet antigen-2
IADPSG *see* International Association of Diabetes and Pregnancy Study Groups
IAPP *see* islet amyloid polypeptides
iatrogenic diabetes side effects 343–344, 347
iatrogenic gastroparesis 801
iatrogenic hypoglycaemia 473, 579–587
iatrogenic infections 893–894
iatrogenic skin conditions 838–839, 849–850
ICAM-1 *see* intercellular adhesion molecule 1
ICC *see* interstitial cells of Cajal
ICCF *see* Innovative Care for Chronic Conditions Framework
ICD *see* implantable cardioverter-defibrillators
Iceland 62, 167, 190, 192
IDDM *see* Insulin-Dependent Diabetes Mellitus
IDF *see* International Diabetes Federation
IDR *see* interdecile range
IFCC *see* International Federation of Clinical Chemistry
IFG *see* impaired fasting glucose
IFN *see* interferons
IGF-1 *see* insulin-like growth factor 1
IGF-2 *see* insulin-like growth factor 2
IGT *see* impaired glucose tolerance
IHSG *see* International Hypoglycaemia Study Group
imeglimin 1156–1157
immune checkpoint inhibitors 216–219
immune homeostasis 262
immune modulation 218–219, 1133–1134, 1148–1149
immune response 437, 692
immune system
gene therapy 1148–1149
infections 878–883, 892–894
immunization, travel 968
immunogenicity 528–529
immunohistochemical studies 49
immunosuppression 473–488
immunotherapies
antigen-specific therapy 133
anti-thymocyte globulin 1130–1131
autoimmune Type 1 diabetes 1125–1136
β-cell autoantibodies 1125–1134
biomarkers 1113–1134, *1135*
CD blockade 1128–1131
current status 1133–1134
future directions 1125–1136
heterogeneous diseases 1133–1134
human leucocyte antigen complex 1125–1126
inflammation 1126–1128, 1131–1133
insulin 1126–1134
interleukins 1126–1128, 1131–1133
safety 1129–1133
tumour necrosis factor-α 1126–1128, 1132
Type 1 diabetes 1125–1136
impaired fasting glucose (IFG) 24
impaired glucose tolerance (IGT) 23–24, 55–71, 382, 390–392
impaired incretin effect 231–232
impaired insulin-stimulated muscle glycogen synthesis 238, 240–242
implantable cardioverter-defibrillators (ICD) 740

IMPROVE-IT trial 717, 728
IMT *see* intima-media thickness
incretin effect 231–232, 492–493, 508–511, 514–515, 521–522
incretin hormones
  β-cell function 231–232
  gastrointestinal tract 80–81, 84, 89, 93–96
  oral glucose lowering drugs 492–493, 508–511, 514–515
  Type 2 diabetes 232
incretin mimetics 534, 537–548
incretins
  cancers 867, 872–873, 875–876
  microvascular complications 615–616, 619, 625–626
  signalling 261, 266–267
  Type 2 diabetes 232, 534, 537–548, 1154–1164
India
  burden of diabetes 29–30, 32–34, 36
  chronic pancreatitis 320, 323
  culture/ethnicity/religion 987–991
  end-of-life care 1085
  exercise 390–392
  genetics of diabetes 157–158, 160
  gestational diabetes mellitus 1056
  global burden of diabetes 29–30, 32, 34, 36
  infections 887
  insulin resistance 243
  LMIC care models 1108, 1112
  social determinants 975–976
  tuberculosis 887
  Type 1 diabetes 29, 44, 46, 217, 223
  Type 2 diabetes 55–56, 60–65, **70**, 222–223
Indian Diabetes study **392**
Indians (First Nations) 976–978
indigenous populations
  global burden of diabetes 30–31
  retinopathy 1101–1102
  social determinants of diabetes 973, 976–978, 981
  Type 1 diabetes 44
  Type 2 diabetes 61–62, 65–67
indirect blood glucose sensing 134–135
indirect glucotoxicity 683–684
Indonesia 67, 323, 887–888
induced pluripotent stem cells (iPSC) 1137–1139
inequality aspects 973–981, 991, 1111–1112
infant feeding 50
infections 333, 878–898
  see also Covid-19 pandemic
  AIDS 878, 882–883, 887
  animal studies 880–881
  antiretroviral therapy 151, 299, 878, 883–884
  bactericidal activity 878, 880–881, 888–892
  bidirectionality of 882–884
  blood glucose 878, 881–883, 893–894
  bone disorders 893
  cardiovascular disease 878–894
  chemotaxis 845, 878, 880–881
  cholecystitis 890
  cystitis 878, 889–891
  diabetic ketoacidosis 602–606
  emphysematous pyelonephritis 878, 888–891
  endophthalmitis 884–885
  epidemiology 878–879, 888
  foot disease 771–778, 878–893
  Fournier gangrene 878, 892–893
  fungal 336, 838–839, 845–848, 878, 881–882, 890–891
  gastrointestinal tract 890–891
  general care principles 894
  global burden of diabetes 34–35
  glycaemic levels 879–894
  head 218, 313, 884–885
  hepatitis C 878, 882–883
  HIV 151, 299–300, 878, 882–883, 886–887
  host factors 880–882
  hyperglycaemia 879–894
  hyperosmolar hyperglycaemic syndrome 602, 608–610
  immune system 878–883, 892–894
  innate immune system 878–882, 887
  insulin therapy 893–894
  intra-abdominal infections 890–891
  joints 893
  kidneys 878–879, 893–894
  macrophages 878–881
  malignant otitis externa 845, 878, 884
  management 880–888, 892–894
  monocytes 878–881
  morbidity 878–879, 883–885
  mortality 878–879, 884–894
  mucormycosis 878, 884, 891
  neck 218, 313, 884–885
  necrotizing fasciitis 333, 845, 878, 892–894
  neuropathy 878–881, 888–894
  neutrophils 878–882, 888, 891
  obesity 878–883, 886–887
  organism-specific factors 881–882
  pathogenesis 878, 881–882, 885, 889
  periodontal disease 338, 810–818, 885
  peripheral arterial disease 878–881, 893
  phagocytosis 878–882, 891
  prevention strategies 894
  respiratory tract 885–888
  sexual dysfunction 791
  skin conditions 838–840, 844–850, 878–882, 890–893
  soft tissue 878–879, 884–885, 891–893
  subcutaneous tissue 891–893
  tuberculosis 878, 880–881, 885–888, 894
  urinary tract 878–881, 888–891, 926
  vaccinations 878, 880, 888, 894
  vascular disease 878–894
  viral 878, 882–886, 894
inferior petrosal sinus sampling (IPSS) 311
inflammation 681–696
  atherosclerosis 692
  gene therapy 1144, 1146–1150
  heart failure 732, 734
  immunotherapies 1126–1128, 1131–1133
  pathogenesis 681–696
  pathways 244, 265, 684, 814
  Type 1 diabetes 1126–1128, 1131–1133
influenza 888
information technology 1099–1101, 1109, 1116–1118
ingrowing nails 848
inhaled insulins 16, 436–437, 441
inherited lipodystrophy 275, 278, 288–291
inherited progressive hyperglycaemia 275, 280–285
in-hospital hyperglycaemia 560–561, 563–566, 570–574
in-hospital hypoglycaemia 559–572, 574–575
in-hospital treatments
  admission 571–573, 575
  blood glucose 574
  communication skills 570–571
  discharge 573–575
  emergency surgery 574
  end-of-life care 575
  evidence-based medicine 570
  foot care 575
  glucocorticoids 574
  glucose concentrations 559, 561–562
  glycaemic levels 559–575
  hyperglycaemia 559–566, 570–575
  hypoglycaemia 559–572, 574–575
  inpatient care 35–36, 352, 559–578, 922, 945–947, 1004, 1102
  insulin 565–567, 574–575
  length of stay 562, 568
  medication factors 565
  monitoring 574–575
  operating theatres 573
  patient safety 562–563
  patient satisfaction 563–564
  perioperative aspects 570–572
  postoperative aspects 570, 573–574
  recovery 573–574
  safety 562–563
  satisfaction aspects 563–564
  self-management 563
  staff education 564
  standards 562–564
  steroid therapies 574–575
  surgical management 559–578
  technology 565
initial consultation impacts 330
injection regimes
  basal-bolus injections 434, 440–441, 999, 1006
  current recommendations 431
  daily injections 431, 434, 459–470
  injection sites 431, 435–437, 442, 529
  mealtime injections 431, 433, 436–441
  multiple daily injections 431–434, 445–454, 459–470, 593–594, 1058
  once-daily injections 431, 439, 441
  sexual function 780, 786, 788
  twice-daily injections 431
innate immunity
  infections 878–882, 887
  mannose-binding lectins 622–625
  microbiome 265–266
  pathogenesis 615, 619, 622–625, 681, 692–693
Innovative Care for Chronic Conditions Framework (ICCCF) 1115
inositol 93, 103, 121, 659–660
in-patient care 35–36, 352, 922, 945–947, 1004, 1102
  see also in-hospital treatments
insomnia 898–901
insulin
  see also insulin. . .

insulin (*cont'd*)
action 111–127, 311–312, 1154, 1160–1161
allergies, skin 849
autoantibodies 25, 203–213
autoimmune Type 1 diabetes 203–213, 1126–1134
biosynthesis 85–89
cancers 867–876
carbohydrates 368, 372
clamp technique 3, 13, *229*, *702*
Cushing syndrome 311–312
deficiency 438–439
definitions 431
dietary factors 368–376
discovery 9–11, 431–432
dosage 604–608
ectopic production 1146
excess *see* hypoglycaemia
exercise 376, 382–400
faster insulin aspart 434, 572, 1006–1007, 1046
gene mutations 15, 160, 220–221, 231, 1147
gene therapy 1144–1151
glucose metabolism 77–82
glucose transport 117–118
heart failure 742
heterologous regulation 118–121
hyperglycaemia 348, 459–463, 468–469
hypoglycaemia 459–470, 579–597
immunotherapies 1126–1134
in-hospital treatments 565–567, 574–575
islet cell transplantation 473–484
mechanism of action 111–127, 311–312, 1154, 1160–1161
microRNA-mediated regulation 119
mimetic agents 1160
nutrients 111–112, 116–124
pancreatic β-cells 111–112, 116–124
pancreatic diseases 319–328
physical activity 382–400
pregnancy 1046
promotion factors 79, 220, 281, 683, 1146
receptors 112–122, 275, 288–291
release/storage 85–89
replacement 1138–1140
signalling 114–124, 261, 265–269
skin reactions 849–850
stem cell therapy 1138–1140
structure of 112
Type 1 diabetes 41–43, 47–51, 203–213, 384–389, 1126–1134
Type 2 diabetes 68–70, 111–112, 116–121, 534–548, 1154–1165
units of 435
whole pancreas transplantation 473–484
insulin analogues 579, 593–595, 1034, 1045–1046
insulin aspart 1034, 1046
insulin degludec 434, 461, 540–542, 593, 742, 1006, 1046, 1089
Insulin-Dependent Diabetes Mellitus (IDDM) study 23, 70, 383–384, 389, 516, 537
insulin-dependent glucose 136–137
insulin detemir 1034, 1046
insulin glargine 434, 461, 540–543, 726, 742
insulin-independent glucose 125, 136–137
insulin-like growth factor 2 (IGF-2) 111–113, 117, 157, **163–165**, **168–173**, **176**, 190
insulin-like growth factor I (IGF-I) 82, 111–124, 306
insulin-like peptides 111, 128–129
insulin lispro 433–435
insulin mixtures 440–441
insulin neuritis 658, 947
insulinotropic agents 1154, 1156–1159
insulin pens 435–436, 441–446, 460, 468
insulin pumps
adverse events 469
basal rates/patterns 459, 461–463
bolus advisors 459, 463–464
children 999–1002, 1005–1014
continuous glucose monitoring 459–470
end-of-life care 1090–1091
evidence-based medicine 465–468
glucose monitoring 444–451, 457, 459–470
hypoglycaemia 579, 587, 593–597
infusion set novel technologies 459, 468
in-hospital treatments 574
intraperitoneal 459, 469–470
novel technologies 431, 434–439, 459–470
patches 459, 468–470
sensor-augmented therapy 431, 438, 464, 474, 597
travel 968
insulin receptor substrate-1 (IRS1) 192–193
insulin receptor substrate (IRS) proteins 111–122
β-cell function gateway 124
degradation regulation 120–121
downstream signalling cascade 114–115
future drug treatments 116
gateway to β-cell function 124
insulin action 114–124
lipid phosphates 121
normal physiology 111–122
protein regulation 121
Ser/Thr phosphorylation 119–120
signalling cascade 114–124
transcriptional control 118–119
insulin regimes *see* insulin therapy
insulin-regulated glucose transport 117–118
insulin resistance
acanthosis nigricans 275–276, 282, 288–290
adipose tissue 238, 244–247
adolescents 1020–1022
age-related incidence 241–242
amelioration 1149
ATP synthesis 242–244
cellular mechanisms 238–240
clinical features 289
complications 681, 684
definitions 238–240
dietary factors 240
drug-induced diabetes 295, 297–299
ectopic fat storage 238, 240, 245–246
fasting hyperglycaemia 238, 245
gene therapy 1144, 1149–1151
genome-wide association studies 243
glucose transport 238–247
hepatic gluconeogenesis 238–239, 245–247
heterologous regulation 118–121
hyperglycaemia 238, 240–247, 684
hypersecreting endocrine disorders 304–309, 315–317
impaired insulin-stimulated muscle glycogen synthesis 238, 240–242
insulin action 111–112, 117–124
insulin receptor gene variants 289–290
lipids 240–241, 244–245
liver 242–244
macrophage-induced adipose tissue lipolysis 238, 245–247
management 290
measurements 238–240
mitochondrial function 238–247
monogenic diabetes 275–282, 288–291
muscle glycogen synthesis 238, 240–242
NAFLD 242–247, 820–822, 825–832, 835
normal physiology 111–112, 117–124
nutrition 246–247
obesity 250–258, 1150
older patients 1073, 1075–1076, 1079, 1082
oral glucose lowering drugs 492–496, 499, 504–507, 511–518
protein ingestion 241
risk factors 240
skeletal muscle 238, 240–242
stroke 747–748
tissue-specific 246–247
transition to adulthood 1020–1022
Type 1 diabetes 290
Type 2 diabetes 238–249, 290, 438–439, 1154–1155, 1160–1162
Insulin Resistance Intervention after Stroke (IRIS) trial 726
insulin secretion
acetylcholine 93
adenosine triphosphate 90–92, 225–226
adipokines 89, 95–96
adipose tissue 84, 94–96
amino acids 86–89, 92–95
ATP-sensitive potassium channels 90–92
autonomic nervous system 84, 89, 93–96
β-cells 84–96, 225–237
bile acids 95
calcium 91–92
cholecystokinin 95
decretins 95
diacylglycerol 91–92
drug-induced diabetes 295–302
fat ingestion 227
gastrointestinal tract 84, 89, 93–96
GLP-1 94–95
glucagon 93–95, 105
glucose homeostasis 128–132, 135–139
glucose metabolism 78, 81–82, 84–96
glucose transport 225–228
gut-derived factors 94–96
hormones 84–89, 93–96
incretin hormones 84, 89, 93–96
intracellular effectors 89–92
intra-islet signalling 105
islet function 84–98
islet hormones 92–94
management 232–233
membrane depolarization 90–92
neural control 93–96
neuropeptides 84, 89, 94–96

neurotransmitters 84–85, 88–95
non-nutrient regulation 92–96
norepinephrine 93
normal physiology 84–98
nutrients 84, 87–96
older patients 1073, 1082
pancreatic islets of Langerhans 227
pathogenesis 225–237
potassium channels 90–92
progressively worse 230
protein ingestion 227
regulation 89–96
Type 2 diabetes 225–237, 534–540, 547–548
insulin sensitivity
body weight 144–145, 150
drug-induced diabetes 296–301
glucose homeostasis 128, 130, 136–138
microbiome 264–265
pregnancy 1035, 1049, 1065
treatment in clinical practice 534–535, 547–548
insulin signalling
action 115–117, 121–124
adipose tissue 123–124
cascade 114–124
forkhead box O subfamily 117, 122–123
glucose homeostasis 123
G-proteins 124
hepatic insulin receptors 122–123
mechanistic target of rapamycin 116–117
microbiome 261, 265–269
mouse genetics 121–124
phosphatidylinositol 3-kinase 115–116
skeletal muscle 123
tissue-integrated 121–124
tyrosine kinases 111–115, 121
insulin-stimulated muscle glycogen synthesis 238, 240–242
insulin therapy
see also continuous subcutaneous insulin infusion
adolescents 1019–1020, 1026, 1029–1031
assessment importance 437–438
automated insulin delivery 431, 438, 464
behavioural factors 918
β-cells 432, 436, 438–439
biosimilars 435, 437, 540
children 999–1002, 1005–1014
clinical presentation 331–334
closed loop 444–445, 453–457, 579, 593, 597, 1007–1008, 1034–1035
combination insulins 440–441
community pathways 441–442
complications 437, 467
continuous glucose monitoring 444–470
cost-effectiveness 467–468
definitions 431
delivery novel technologies 431–472
diabetic ketoacidosis 604–608
discovery of insulin 431–432
education 437–438
end-of-life care 1085, 1087–1093
endogenous insulin secretion 438
exogenous administration 438–439
future perspectives 441–442, 470
GLP-RA 431, 438–441
glucose-dependent action 441–442
hepatoselectivity 441–442
historical perspectives **15**, 16–17, 431–432
hybrid closed loop 444–445, 454–457, 579, 593, 597, 1007, 1034–1035
hyperosmolar hyperglycaemic syndrome 602, 608–610
infections 893–894
intermediate-acting insulins 433–435
intravenous infusions 566, 602, 609–610, 1003
late complications 467
long-acting formulations 431, 434–441
management 431–472
modern formulations 432–435
nephropathy 650–651
novel technologies 431–472
observational studies 459, 465–469
outpatient pathways 441–442
personalized selection techniques 439–441
physiological insulin delivery 432–435
pregnancy 1034–1036, 1045–1049, 1058–1059, 1062
premix insulins 440–441
psychosocial aspects 918
quality of life 467
randomized controlled trials 459, 463–468
rapid-acting preparations 431, 433–437, 440–441
route aspects 441–442
selection techniques 439–441
short-acting formulations 433–435, 437
soluble insulin 431–436
starting insulin 441
subcutaneous infusion 433–442, 459–470, 565–567, 1003–1007
syringes 435–436, 441–442
titrating insulin 441
transition to adulthood 1019–1020, 1026, 1029–1031
travel 968–970
Type 1 diabetes 431–433, 436–442, 459–470
Type 2 diabetes 438–441, 466–469, 534–548, 1154–1165
ultra-long-acting analogues 431, 434
ultra-rapid-acting analogues 431, 434, 440
insurance 956, 962–963, 967–968
integrated healthcare 1097–1099, 1102–1105, 1113–1114, **1117**
intensive care units 561
intensive therapies 664
InterAct Study 56
intercellular adhesion molecule 1 (ICAM-1) 684, 1149
interdecile range (IDR) 454
interferons (IFN) 1126, 1128
interleukins 1126–1128, 1131–1133
intermediate-acting insulins 434
intermediate hyperglycaemia 23–24
intermittent claudication pain 657
intermittently scanned CGM (isCGM) 446–448, 452–455, 593
internal hernias 556
International Association of Diabetes and Pregnancy Study Groups (IADPSG) 26–27, 336, 1035, 1050–1063
International Diabetes Federation (IDF) 23, 28–30, 34, 55, 58–62, 68, 406, 562–563, 810, 817, 1035–1036
International Federation of Clinical Chemistry (IFCC) 24
International Hypoglycaemia Study Group (IHSG) 591–592
international in-hospital treatment guidelines 559, 562, 575
International Normalized Ratio (INR) 753
International Society for Pediatric and Adolescent Diabetes (ISPAD) 327, 910, 1002, 1011–1015, 1020
interquartile range (IQR) 457
interstitial cells of Cajal (ICC) 797–799
interstitial glucose 449–450
intestinal agents 1155–1156
intestinal microbiome 81, 145, 261–271
bile acids 261, 267–268
body weight 145, 261–263
dietary factors 261–267
enteroendocrine cell function 261, 266–269
environmental factors 261–263
farnesoid X receptors 261, 267–268
gastrointestinal tract 81, 261–269
glucagon-like peptides 266–268
glucose metabolism 81
glycaemic control 261, 264–267
host immune development 268–269
hygiene 261, 268
incretin signalling 261, 266–267
innate immune pathways 265–266
insulin sensitivity 264–265
insulin signalling 261, 265–269
intestinal permeability 261–264, 268
lipopolysaccharides 264–269
metabolic endotoxaemia 261–264, 268–269
metabolic function 262–269
permeable intestinal mucosa 261–264, 268
intestinal permeability 261–264, 268
intima-media thickness (IMT) 309, 481, 501, 748
intra-abdominal infections 890–891
intracavernosal injection therapy 780, 786, 788
intracellular effectors 89–92
intracellular factors 615–616, 619–622, 625
intra-islet functions 84–85
intra-islet signalling 99, 101, 105
intramyocellular triacylglycerols 240–241
intraperitoneal insulin pumps 459, 469–470
intra-retinal microvascular abnormalities (IRMA) 631–632
intrauterine contraceptive devices (IUD) 792
intrauterine effects 55–58, 64, 70–71, 160, 192, 936
intravenous fluids 604–606
intravenous insulin 565–567, 602, 609–610, 1003
intravenous lidocaine 667
intravenous recreational drug use 966
intravitreal angiostatic treatment 629, 634, 637–638
inverse care law 35
i-Port system 460–461
iPSC *see* induced pluripotent stem cells
IPSS *see* inferior petrosal sinus sampling

IQR *see* interquartile range
Iran 65, 167, 190
Ireland 62, 771, 957, 960, 1035
Ireland, John 16
IRIS *see* Insulin Resistance Intervention after Stroke
IRMA *see* intra-retinal microvascular abnormalities
iron deposition 319, 325–326
irritable bowel syndrome 796–797
IRS1 *see* insulin receptor substrate-1
IRS *see* insulin receptor substrate
isCGM *see* intermittently scanned CGM (isCGM)
ischaemic cerebrovascular disease 745–754
ischaemic heart disease 724–731
  anticoagulation 729–730
  arterial hypertension 724, 729
  aspirin 724, 729
  atherosclerotic cardiovascular disease 724–730
  blood pressure 724, 729
  cardiovascular disease 724–730
  cholesterol 724, 727–729
  clinical presentation 334–335
  epidemiology 724
  GLP-1RA 724–727, *729*
  glucose levels 724–726
  high-density lipoproteins 724, 727–729
  hormone replacement therapy 793
  hypertension 724, 729
  low-density lipoproteins 724, 727–729
  multi-modal therapy 730
  pathophysiology 724–725
  pregnancy 1043
  risk factors 724–730
  SGLT-2 inhibitors 724–727, *729*
  Type 1 diabetes 724–728
  Type 2 diabetes 724–730
ischaemic stroke 745–754
islet amyloid polypeptides (IAPP) 231
islet antigen-2 (IA-2) 203–204, 208, 1126
islet cells
  see also β-islet cells; islet cell transplantation
  adenosine triphosphate 90–92
  adipokines 89, 95–96
  adipose tissue 84, 94–96
  α-cells 77–78, 84–85, 93–94, 99–108, 111–113, 1139
  amino acids 86–89, 92–95
  amylin 520, 529–530
  anatomy 84, *85*, 99–101
  antibodies 25, 203–213, 216, 999–1000, 1125–1134
  ATP-sensitive potassium channels 90–92
  autoimmunity 203–213, 1125–1134
  autonomic neuropathy 84, 89, 93–96, 101–102
  bile acids 95
  biology 99–101
  calcium 91–92
  δ-cells 78
  cholecystokinin 95
  chronic stimulation 231–232
  decretins 95
  defects 225–237
  destruction 25, 41, 203, 206, 261, 268–269
  development 99–101
  dysfunction 128–130, 136–137, 225–237, 275–287
  failure 13, 26, 227–230
  function 77–81, 84–98
  gastrointestinal tract 84, 89, 93–96
  gene therapy 1147–1148
  genetics 157–158, 190–193
  GLP-1 production 105–106
  glucagon 93–95, 99–108
  glucose homeostasis 128–130, *134*, 139
  glucose metabolism 77–81, 84–96
  hormones 84–89, 93–96
  hyperglycaemia 230–232
  hyperlipidaemia 230–231
  hypoglycaemia 579–588, 593
  incretin hormones 84, 89, 93–96, 232
  insulin action 111–112, 116–124
  insulin biosynthesis 85–89
  insulin secretion 84–98
  insulin therapy 432, 437, 438–439
  intracellular effectors 89–92
  mass 229–230, 233–234
  membrane depolarization 90–92
  metabolic regulation 99–110
  monogenic diabetes 275–291
  neural control 93–96
  neural regulation 100
  neuropeptides 84, 89, 94–96
  neurotransmitters 84–85, 88–95
  non-nutrient regulation 92–96
  nutrients 84, 87–96
  obesity 250, 252–255
  oral glucose lowering drugs 492–494, 501–504, 508–511
  physical activity 389–390, 396
  potassium channels 90–92
  regeneration 1148
  regulation 89–96
  reprogramming 1147–1148
  secretion regulation 101–102
  stem-cell therapies 1137–1143
  structure 84–89
  subunits 111–113
  Type 1 diabetes 203–212, 389–390, 1125–1134
  Type 2 diabetes 13, 26, 157–158, 190–193, 225–237, 396, 1156–1160
islet cell transplantation 473–488
  β-cell replacement 473–477, 485–488
  bleeding 487
  challenges 485–488
  chronic immunosuppression 487–488
  clinical outcome assessments 481–482
  competing therapies 482–485
  genetic engineering 1145–1146
  glycaemic management 473–488
  grafts 473–488
  historical perspectives 476–477
  hypoglycaemia 473–484, 488
  IAK 484
  immunosuppression 473–488
  indications 479
  insulin independence 473–484
  ITA 482–485
  management 473–491
  morbidity 481
  mortality 473, 479–483
  nephropathy 473, 480, 482
  neuropathy 473, 480, 482
  organ source 485
  outcome assessments 479–481
  PAK 484
  peri-procedural care 473, 485–488
  portal thrombosis 487
  potential solutions 485–488
  preservation 485
  procedural considerations 477–479
  PTA 482–485
  retinopathy 481–482
  SIK 482–484
  SPK 482–485
  state of the art aspects 481–482
  stem-cell therapy 485, 1140
  survival 473–488
  tissue source 485
  Type 1 diabetes 473–487
  vascular disease 473, 476–487
  whole pancreas transplantation 473–491
islet hormones 92–94
islets of Langerhans 77–78, 84, *89*, 96, 227
  see also islet cells
ISO 15197:2013 standards 445
isophane insulin 16, 434, 539, 575, 1046, 1089, 1093
isosorbide dinitrates 667
ISPAD *see* International Society for Pediatric and Adolescent Diabetes
Israel 46–47, 918, 1053
ITA 482–485
Italy 42–47, 63, 344, 467, 469, 829
IUD *see* intrauterine contraceptive devices
Ivo Drury 19

Jaeger, Eduard von 8
Jamaica 62, 1115
Janus kinase (JAK) 120–121, 199, 426, 844
Japan 45–46, 61, 66, 218, 251, **391**, 396, 656, 664–665, 748, 1036
jaundice 199, 319, 504, 890, 1040
Joint British Diabetes Societies (JBDS) 561–562, 570
joint disorders 853–858, 893
Jordan 790
Joslin, Elliott P. 8–11, 15, 18–19
c-Jun NH2-terminal kinase (JNK) 265–266
Juvenile Diabetes Research Foundation (JDRF) 450, 592, 683
juvenile-onset diabetes *see* Type 1 diabetes

Kaleidoscope model of care 345–346
KANWU trial 374
Kaplan–Meier curves 709–710
KCJN11 167
KCNJ11 283–286
KDIGO *see* Kidney Disease: Improving Global Outcomes
Kearns–Sayre syndrome 317
Keen, Harry 18
ketamines 966
ketoacidosis, diabetic (DKA)
  acute metabolic complications 602–608
  adolescents 1027–1028
  behavioural factors 907, 911–912

care aims 343, 346–347, 351
causation aspects 604–605
cerebral oedema 1003–1004
children 999–1007, 1010
classification 23, 25–26
clinical presentation 330–334, 338, 605, 1002
definitions 602–603
diagnosis 23–26, 603–608, 1002
drug-induced diabetes 295, 301
electrolytes 604, 607
end-of-life care 1085–1090
fluid disturbance 604
fluid therapy 604–606
global burden of diabetes 33
glucagon 99
historical perspectives **4**, 18
hyperglycaemia 604
infections 602–606
insulin therapy 604–608
intravenous fluids 604–606
ketogenesis 604
ketonaemia 602–607
Kussmaul breathing 605, 999, 1001–1002
management 602–608, 1002–1004
metabolic acidosis 602–608
osmotic diuresis 603–607
pathogenesis 216–218, 603–608
pathophysiology 603–608
precipitating factors 604–605
pregnancy 1036–1037, 1041
prevention strategies 607–608
psychosocial aspects 907, 911
resolution 607–608
severity 603–607
SGLT-2 inhibitors 604
transition to adulthood 1027–1028
Type 1 diabetes 216, 218, 602–608
Type 2 diabetes 602–604
ketogenesis 604
ketonaemia 602–607
ketones 77, 410, 968, 1010–1013
ketosis 26, 59, 217–219, 223
Kidney Disease: Improving Global Outcomes (KDIGO) 641–642, 645–648
kidney disease
see also nephropathy
biomarkers/precision medicine 414–426
care aims 350–351
complications 615–626, 640–654
glucose metabolism *78*, 81–82
heart failure 734
infections 878–879, 893–894
kidney failure 640–652
kidney–pancreas transplantation 640, 646, 648–651
NAFLD 820, 828–831
outcomes trials 545–546
replacement 640, 643–648, 651
risk factors 644–645
stem-cell therapy 1142–1143
transplantation 640, 646, 648–651
Type 2 diabetes 534–537, 541–548, 640–652
Kimmelstiel, Paul 13–14
Kimmelstiel–Wilson syndrome 13–14
KINDL-R tool 913
King's Obesity Staging Criteria 251–252
Klebsiella infections 882
Korea 66
Kussmaul, Adolf **4**, **6**
Kussmaul breathing (respiration) 333, 602, 605, 999, 1001–1002
Kuwait 30, 42, 44, 64–65, 467
Kyrgyzstan 1108, 1110, 1114, 1116

labour and pregnancy 1048–1049
lactates, glucose metabolism 77, 80, 82
Lactobacillus spp. 263–264, 1156
Lacunar infarct, stroke 746
Lacy, Paul 13–14
LADA *see* latent autoimmune diabetes in adults
Laguesse, Gustave 8
Lancereaux, Etienne 8, 12
Lane, M.A. 14
Langerhans, Paul 8
language aspects 361, 922–930, 988, 996
Laser doppler imaging FLARE (LDI FLARE) 663
laser photocoagulation 18, 480–482, 958–959
laser therapy 668
latent autoimmune diabetes in adults (LADA) 25, 157–159, 194, 217–218
Latin America 68–69, 221, 1057, 1113
Lawrence, Robin D. 19–20
laxatives 796, 807–808
LDI FLARE *see* Laser doppler imaging FLARE
LDL *see* low-density lipoproteins
leadership in care 1110, 1117–1118
LEADER study 16, 415–416, 527, 542–543, 547, 591, 694, 727, 737
leaving home factors 957, 970–971, 1019–1021, 1025
left ventricular ejection fraction 732, 740–742
legacy effect 616–618, 683–684
Legionella infections 885
legs *see* lower-limb symptoms
lente insulin 462
lentiviral vectors 1146, 1148–1149
leptin receptors 147, 199, 231
leptins 147, 199–200
lesions 629–637, 772–774
LGI *see* low glucose index
licences, driving 959–961
lichen planus 846
Lichtenstein, Adolf 17
lidocaine 667
life expectancy 142, 151, 1072, 1075–1077, 1080–1083
see also mortality
lifestyle factors
body weight 551–552, 556–557
care aims 343–344, 351
cultural aspects 992, 994–995
dietary factors 368–371
gestational diabetes mellitus 1058, 1063–1066
heart failure 735–736
historical perspectives **15**
microbiome 261
NAFLD 832
neuropathy 664
older patients 1075–1076
oral glucose lowering drugs 492–496, 500–501, 504–507, 510–513, 517–518
patient education 354
pregnancy 1058, 1063–1066
sexual dysfunction 789
stroke 745, 752–753
Type 2 diabetes 68
life-threatening emergencies 343, 351
life-threatening infections 878, 884, 888–893
LIFE trial 690, 708, 749
limbs *see* lower-limbs; upper limbs
limited joint mobility 853–854
linagliptin 492, 496, 509–510, 726
LincRNAs 192
linkage studies 157, 160, 167, 190
lipid phosphates 121
lipids
biomarkers/precision medicine 423–425
hormone replacement therapy 793
insulin resistance 240–241, 244–245
ischaemic heart disease 724, 727–729
lowering drugs 298, 350, 423–425, 650, 714–720, 834–835, 1162–1163
metabolism 79, 99, 102–107
NAFLD 821–835
nephropathy 650
neuropathy 655–656, 670, 673
obesity 250–251, 254–256
profiles 705, 717–718, 793
stroke 749
lipoatrophy 849
lipodystrophy 275, 278, 288–291, 295, 299–300
lipohypertrophy 849
lipolysis 82–83, 121–124, 243–247, 514–516, 560, 603–604, 826–828
lipopolysaccharides (LPS) 264–269
lipotoxicity 732, 734
liraglutide 256–257, 420–421, 525–530, 553–554
see also glucagon-like peptide 1 receptor agonists
Lithuania 43, 51
liver disease
see also non-alcoholic fatty liver disease
abscesses 890–891
biopsies 325, 821–824
body weight 142, 145, 151
failure 820, 829, 835
glucagon 102–105
glucose homeostasis 129–134, 138
glucose metabolism *78*, 79–80
insulin resistance 242–244
liver enzymes 516, 822–825, 833–834
liver fat (steatosis) 821–828, 832–834
liver fibrosis 820–835
liver stiffness 823–825
liver transplantation 547, 570, 829
lixisenatide 525–528, 538, 541–543
LMIC *see* low-and middle-income countries
LMNA, monogenic diabetes 275, *277*, 291–292
long-acting insulin formulations 431, 434–441
long distance travel 968
Look AHEAD study 396, 551, 557, 706, 716, 735–736, 1076
loop diuretics 539, 708

Loubatieres, Auguste 16–17
low-and middle-income countries (LMIC)
  access universality 1109, 1114, 1116, **1118**
  care models 1107–1121
  comorbidity 1110–1111
  continuity of care 1114–1115, **1118**
  Covid-19 pandemic 1110–1111
  current challenges 1107, 1109–1112
  definitions 1108
  diagnostics tests 1116–1117
  education 1116
  equality 1111–1112
  finance aspects 1110, 1117–1118
  global burden of diabetes 28–37
  governance 1110, 1117–1118
  health systems 1108–1118
  HIV/AIDS 1108, 1110, 1113–1117
  human resources 1109, 1116–1118
  individual, focus on 1115–1116
  information aspects 1109, 1116–1118
  innovation 1116–1117
  integration 1113–1114, **1117**
  leadership 1110, 1117–1118
  medical products 1109, 1116–1118
  mortality 1110–1113
  needs-based approach 1115
  non-communicable diseases 1108–1117
  novel technologies 1116–1117
  policy aspects 1113–1115
  quality factors 1114–1115, **1118**
  responsiveness 1114–1115, **1118**
  service delivery 1109–1118
  tuberculosis 1110, 1116
  Type 1 & 2 diabetes 1108–1118
  United Nations 1108, 1114
  vulnerable population challenges 1111
  ways forward 1107–1108, 1112–1118
low-calorie/energy diets 255–256, 551–552
low-density lipoproteins (LDL) 423–426, 682–686, 690–692, 695–696
  body weight management 551, 554
  cardiovascular disease 256, 713–721, 724, 727–729, 1101
  children 1015
  dietary management 373–375
  hormone replacement therapy 793
  hypertension causation 701, 705
  hypoglycaemia 597
  ischaemic heart disease 724, 727–729
  islet cell transplantation 481–482
  monogenic causes of diabetes 281–282
  NAFLD 825, 831, 834–835
  physical activity 389
  stroke 752
lower-limb symptoms
  amputations 32–33, 771–779
  foot disease 655–664, 667–671, 771–779, 1102
  global burden of diabetes 32–33
  ischaemia 760–761
  peripheral vascular disease 757, 760–761
  skin conditions 842–844
low glucose index (LGI) 452
low glucose suspend 464, 593, 918, 1010–1012
low-intensity laser therapy 668
low protein diets 650
LPS *see* lipopolysaccharides
Lundbæk, Knud 13, *14*

M2 macrophage modulation 799–800
MAC *see* membrane attack complex
MACE *see* major adverse cardiovascular events; myocardial infarction and stroke, three-point major adverse clinical event
Mackenzie, Stephen 8
Macleod, J.J.R. 7, 9–12, 432
macrocapsules 1139–1140
macro factors, social determinants of diabetes 973–981
macronutrients 368, 371–375
macrophages
  adipose tissue lipolysis 238, 245–247
  autoimmune Type 1 diabetes 1125, *1128*
  gastrointestinal tract 799–800
  infections 878–881
macrosomia 280–283, 1038–1040, 1044, 1048, 1055–1060, 1063–1064
macrovascular complications
  accelerated atherosclerosis 681, 685–691
  arterial disease 681, 688–690, 755–767, 771–775
  atherosclerosis 681–695
  behavioural factors 907, 912
  biomarkers/precision medicine 414, 418, 423
  cardiovascular disease 681–696, 700–710, 713–723
  cerebrovascular disease 745–754
  classification and diagnosis 22
  clinical presentation 330, 334–335
  coronary artery disease 681, 688–690
  dyslipidaemia 695, 713–720
  endothelial dysfunction 681–696
  global burden of diabetes 32–34
  glucose management 682–696, 713, 715–716
  haemodynamic factors 681–682, 686–687
  heart failure 732–744
  hormonal contraception 792
  hyperglycaemia 682–696, 713, 715–716
  hypertension 694–695, 700–712
  inflammation 681–696
  innate immune system 681, 692–693
  ischaemic heart disease 724–731
  islet cell transplantation 473, 480–482
  mental disorders 933, 937, 943–945, 949
  metabolic factors 681–687
  NADPH 681, 683–685, 691–693
  nephropathy 640–654
  oral glucose lowering drugs 492–495
  osteoprotegerin 681, 692
  oxidative stress 681–685, 688–691
  pathogenesis 681–699
  peripheral vascular disease 755–767
  renal denervation 695
  South Asian populations 990
  stroke 745–754
  whole pancreas transplantation 473, 480–482
macrovesicular steatosis 820–821
maculopathy 335, 629–631, 633–637, 1102
MAFLD *see* metabolic dysfunction-associated fatty liver disease
MAG *see* mean absolute glucose change
MAGE *see* mean amplitude of glucose excursions
MAGIC trial 167, 193
magnesium 607
magnetic resonance angiography (MRA) 761
magnetic resonance elastography (MRE) 823
magnetic resonance imaging (MRI)
  body weight 145, 251
  gastrointestinal tract 804–806
  genetics 159
  hypersecreting endocrine disorders 305, 310
  hypoglycaemia 587–588
  joints 856–858
  malignant otitis externa 884–885
  NAFLD 822–823, 834
  neuropathy 672
  pancreatic disease 319, 326
magnetic resonance imaging–proton density fat fraction (MRI-PDFF) 821–823
major adverse cardiovascular events (MACE) 415–416, 527, 541–546, 694, 715, 726–729
major neurocognitive disorders 926
Malawi 1108
male sexual dysfunction 673–674, 780–790
malignant otitis externa 845, 878, 884
Malmo Study **391**
mandibular hypoplasia, deafness, progeroid features, and lipodystrophy (MDPL) syndrome 291
mania 900, 947
mannose-binding lectins (MBL) 622–625
manometric profiles 804–806, *804*
MAPK *see* mitogen-activated protein kinase
MARD *see* mean absolute relative difference; mild age-related diabetes
Marshall Islands 30
MASP *see* MBL-associated serine proteases
mast cells 841, 854, 880
maternal health
  see also gestational diabetes mellitus; pregnancy
  heritability 192
  hypoglycaemia 1034, 1040–1041, 1049
  Type 2 diabetes 55–58, 64, 70–71
maternally inherited diabetes and deafness (MIDD) 158
maturity-onset diabetes *see* Type 2 diabetes
maturity-onset diabetes of the young (MODY) 283–286
  ABCC8 283–286
  biomarkers/precision medicine 417–418
  causation 275–287
  children 1002
  clinical features 279–282
  diagnosis 275–288
  extra-pancreatic clinical features 281–282
  genetics 157–160, 278–281
  historical perspectives 12–13, 16–18
  insulin action 111–112
  KCNJ11 283–286
  management 280–283
  pregnancy 280–286
  rare subtypes 283
  Type 1 diabetes 219–221, 280, 282

Type 2 diabetes 280, 282
variant prevalence 276–281
Mauritius 30, 45, 64, 66
MBL *see* mannose-binding lectins
MBL-associated serine proteases (MASP) 622–624
MC4R melanocortin-signalling mutations 147, 199–200
MCP-1 *see* monocyte chemotactic protein 1
MDI *see* multiple daily injections
MDPL *see* mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome
MDRD *see* Modification of Diet in Renal Disease
meals, travel 969–970
mealtime injections 431, 433, 436–441
mean absolute glucose change (MAG) 452
mean absolute relative difference (MARD) 448–449
mean amplitude of glucose excursions (MAGE) 452
mechanistic target of rapamycin (mTOR) 116–117
medical care abroad 967–968
medical device skin reactions 850
Medical Outcome Study (MOS-36) questionnaire 913
mediobasal hypothalamus glial cell activation 128, 132–133
Mediterranean diet 56, 63, 374, 716, 832, 1065
meglitinides 492, **496–498**, 505–506, 535, 537–538
Melanesian populations 65
melanin 325, 530
melanocortin-signalling 131–132, 147, 199–200
MELAS syndrome 158, 287
melatonin 192–193
melatonin receptor gene (MTNR1B) 228
melioidosis 882, 885
membrane attack complex (MAC) 622–625
membrane depolarization 90–92
memory
cognitive function 922–929
glycaemic memory 616–618, 683–684
metabolic 192, 646–648, 664, 683–684
Mendelian disorders 197–198
menopause hormone therapy (MHT) 295, 298
mental health 933–955
acute metabolic complications 933, 943–946, 949
adolescents 1022, 1026–1028
anxiety disorders 933–934, 938–942, 945–947
bipolar affective disorder 933–934, 947–948
body weight 933–952
care aims 343, 347, 351–352
comorbidity 933–938, 941–947
complications 933, 936–937, 943–945, 949
depression 907–918, 933–942, 945, 947–949
eating disorders 907, 910–915, 942–947, 1029–1030
environmental factors 933–936, 941, 948–949
genetic factors 933, 937–938, 949
global burden of diabetes 34–35
healthcare teams 933, 938–939, 946–947
morbidity 933–938, 941–947
obesity 933–937, 944–946, 949–952
patient education 362
primary care 933–939, 942
psychotic illnesses 933–934, 947–953
schizophrenia 933–934, 940, 947–952
screening 933–934, 938–939, 942–946, 950–952
transition to adulthood 1022, 1026–1028
Menzel, Ruth 18
MERCI device 750
Mering, Josef von 7
mesenchymal stem cells (MSC) 1138–1139, 1142
mesenteric arteries 478, 761–762
meso factors 973–975, 980–981
MET *see* metabolic equivalent units
metabolic acidosis 602–608
metabolic alteration 145–146
metabolic bone disease 556
metabolic complications/factors 602–611, 615–620, 681–687
advanced glycation end-products 619–620
aldose reductase/polyol pathways 620
diabetic ketoacidosis 602–608
hyperosmolar hyperglycaemic syndrome 602–604, 608–610
macrovascular 681–687
management 602–611
microvascular 615–620
NAFLD 820–835
pathogenesis 615–620, 681–687
polyol pathways 620
skin conditions 838–841
metabolic dysfunction-associated fatty liver disease (MAFLD) 251, 820–822
metabolic endotoxaemia 261–264, 268–269
metabolic equivalent (MET) units 382, 391–392
metabolic function
metformin 499–500
microbiome 262–269
obesity 250–256
sexual dysfunction 782, 789
metabolic memory 192, 646–648, 664, 683–684
metabolic regulation 99–110
metabolic surgery 551–558
metabolic syndrome 56–57, 111, 121, 701–702
metabolism
amylin 529
carbohydrates 78–81, 250, 255, 309–310
circadian control 130
GLP-1 79, 81, 94–95, 522–523
glucose 77–96, 1154–1157
lipids 79, 99, 102–107
myocardial 732–733
nutrients 89–92, 1164
older patients 1075, 1078
reverse 1075, 1078
metabolites 157–159, 261, 263–265, *267*
metagenome sequencing 263
metalloproteinases 507, 688, 823
metformin 68–70, 492, 496–501, 534–548
adolescents 1026–1027
adverse-effects 501
biomarkers/precision medicine 418–420
brain control 139
cancers 867–868, 872–876
efficacy 500–501
glucose homeostasis 139
heart failure 742
historical perspectives 17
indications 500
ischaemic heart disease 726
modes of action 499–500
NAFLD 833
nephropathy 650
pregnancy 1034, 1038, 1047–1049, 1052, 1059, 1064–1066
stroke 749
METSIM study 190
Mexico 34–36, 44–45, 62, 219, 1113
Meyer, Jean de 8
Meyer-Schwickerath, Gerd 18
MHT *see* menopause hormone therapy
Michigan Neuropathy Screening Instrument 664
microalbuminuria 1015
microaneurysms 629–630, 634–637
microbe risk factors 49–51
microbial metabolites 261, 263–265, *267*
microbiome *see* intestinal microbiome
MICRO-HOPE study 690
Micronesia 65, 1108
micronutrients 375
microRNAs (miRNAs) 119, 157, 160, 192
microtubules 88–89
microvascular complications
angiopathy 615–616, 621, 624
arterioles 615–616
behavioural factors 907, 912
biomarkers/precision medicine 414, 418
capillaries 615–616, 624
cardiovascular disease 615–616, 622–626, 669–671
care aims 350–351
clinical presentation 330, 335–336
cytokines 615, 619, 621–622, 625
diabetes classification and diagnosis 22
dipeptidyl peptidase-4 inhibitors 615–616, 626
end-stage kidney disease 640–652
genetic polymorphisms 615, 619, 623–624
global burden of diabetes 33
GLP-1 RA 615–616, 626
growth factors 615, 619, 621–622, 625
haemodynamic factors 615, 619–622
hormonal contraception 792
hyperglycaemia 615–626
innate immune system 615, 619, 622–625
islet cell transplantation 477, 486
kidney disease 615–626, 640–652
mental disorders 933, 936–937, 943–945
metabolic factors 615–620
NAFLD 830–831
nephropathy 615–626, 640–654
neuropathy 615–616, 620, 626, 655–678
oral glucose lowering drugs 492–495
pain 655–674
retinopathy 615–621, 629–640
SGLT-2 inhibitors 615–616, 619, 625–626
South Asian populations 990

microvascular complications (*cont'd*)
Type 2 diabetes 396
whole pancreas transplantation 477, 486
MIDD *see* maternally inherited diabetes and deafness
Middle East
culture/religion 988–990
infections 879, 882, 886
obesity 250, 256
Type 2 diabetes 29–35, 55, 64–65, **68–69**
miglitol 493, 496, 514–516
migration 988, 991, 1111
mild age-related diabetes (MARD) 159
mild obesity-related diabetes (MOD) 159
mindfulness-based therapies 908, 916–917
mindsets, patient education 361, **362**
mineralocorticoid receptor antagonists 649, 732, 739–741
minerals
bone density 390, 396, 508, 556, 793, 853
cardiovascular disease 718–719
children 1008, 1016
exercise 390
mental health 945
micronutrients 375
Type 2 diabetes 1155–1156
Mini Cog test 1080
mini-dose glucagon 1011
Minkowski, Oskar 7–8
minority groups, ethnicity 987–997
MIRKO mice 123
miscarriage 1038–1039
Missouri Pregnancy Risk Assessment Monitoring System (PRAMS) 297
mitochondria 275–277, 281, 286–287, 615, 617
mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS syndrome) 158, 287
mitochondrial function 238–247
mitochondrial glycerol-phosphate dehydrogenase 499–500
mitochondrial mutations 221–222
mitogen-activated protein kinase associated protein 1 (SIN1) 115–116
mitogen-activated protein kinase (MAPK) 115–116, 499, 622, 684–685
MoCA *see* Montreal Cognitive Assessment
MOD *see* mild obesity-related diabetes
Modification of Diet in Renal Disease (MDRD) 641
MODY *see* maturity-onset diabetes of the young
Mogensen, Carl-Erik 18
molecular mimicry 50, 211
MONICA study 63, 656, 745
monitoring
see also continuous glucose monitoring; self-monitoring blood glucose
blood glucose 404–413
children 999, 1004–1015
historical perspectives **15–16**, 17–18
in-hospital treatments 574–575
nephropathy 645
monocyte chemotactic protein 1 (MCP-1) 511, 684–685
monocytes 878–881
monogenic diabetes 275–294
see also specific conditions
autosomal dominant family history 275–291
β-cells 275–291
biomarkers/precision medicine 414–418, 426
children 1002
classification and diagnosis **25**
clinical presentation 281–288, 331–332
diagnosed within 6 months of life 283–286
extra-pancreatic clinical features 281–282, 286–288
genetics 157–160, 275–291
glucokinase gene 275–286
heritability 275–291
hypersecreting endocrine disorders 317
insulin resistance 275–282, 288–291
pancreatic exocrine dysfunction 288
pregnancy 1036
pre-symptomatic molecular testing 279
Type 1 diabetes 219–221, 275–283, 290
Type 2 diabetes 275–282, 285–288, 290–291
monogenic obesity 147–148
mononeuropathy of the limbs 658
monosaccharides *80*, 373
monounsaturated fats (MUFA) 374
Montreal Cognitive Assessment (MoCA) 923
mood disorders 910, 913–919
see also depression
morbidity
body weight 142, 147–148, 150–151
care aims 343–344, 348–349
dementia 923–924, 931
dietary factors 368, 371
gastrointestinal tract 797, 807
heart failure 732–740
infections 878–879, 883–885
islet cell transplantation 481
mental disorders 933–938, 941–947
NAFLD 820, 830, 834
nephropathy 640, 648–651
oral glucose lowering drugs 492, 494
physical activity 382–384, 389
Type 2 diabetes 55, 61–63, 67–68, 534, 538, 541–542, 546–548
whole pancreas transplantation 479
morphological lesions 629–637
mortality
amputations 771
cancers 867–876
cardiovascular disease 713–716, 718–721
care aims 343–344, 348–350
end-of-life care 1085–1087
global burden of diabetes 31–37
heart failure 732, 738–741
hypoglycaemia 568, 596
infections 878–879, 884–894
islet cell transplantation 473, 479–483
LMIC care models 1110–1113
NAFLD 820, 830, 834
physical activity 382–384, 389–393
pregnancy 1034–1043, 1047–1060
sleep 900
stroke 745–746, 749–751
Type 1 diabetes 51–52, 383–384, 1125
Type 2 diabetes 55, 57–60, 67–68, 393
whole pancreas transplantation 473, 479–483
MOS-36 *see* Medical Outcome Study questionnaire
motivational interviewing 1023
motor functions, gastrointestinal tract 797–798
mouse genetics 121–124
Mozambique 1110, 1116
MRA *see* magnetic resonance angiography
MRE *see* magnetic resonance elastography
MRI *see* magnetic resonance imaging
MRI–PDFF *see* magnetic resonance imaging–proton density fat fraction
MSC *see* mesenchymal stem cells
MTNRIB *see* melatonin receptor gene
mTOR *see* mechanistic target of rapamycin
mucormycosis 878, 884, 891
MUFA *see* monounsaturated fats
Mühlhauser, Ingrid 917
multidisciplinary teams 343–352, 926–931, 1097–1105
adolescents 1102–1103
cardiovascular risk factors 1097–1104
care aims 343–352
care models 1097–1101
children 1102–1103
cognitive function 926–931
community care provision 1097–1105
community health workers 1105
community pharmacists 1104
composition 1097, 1103–1105
dementia 926–931
dietitians 1104–1105
education 1098–1099, 1101–1105
family practitioners 1103–1104
foot ulceration 1102
general practitioners 1103–1104
health workers 1105
integration 1097–1099, 1102–1105
nurses 1104
older patients 1072, 1103
pharmacists 1104
practice nurses 1104
pregnancy 1034, 1037, 1043–1044, 1102
primary care 1097–1105
role of 1097–1106
secondary care 1097–1105
self-management 1098–1104
specialists 1097–1105
staff composition 1103–1105
structured education 1098–1099
telemedicine 1098, 1103
Type 1 diabetes 1098, 1104
Type 2 diabetes 1097–1098, 1101–1104
young-onset diabetes 1102–1103
multifactorial management 696, 749
multifocal neuropathy 655–663, 670
multi-modal therapy 730
Multinational Project for Childhood Diabetes 42–45
Multinational Study of Vascular Disease in Diabetes 67
multiple daily injections (MDI) 431–434, 445–454, 459–470, 593–594, 1058

Murray's cure of myxoedema 8
muscle glycogen synthesis 238, 240–242
muscle wasting 288, 333, 772–774
musculoskeletal disease 853–863
  see also bone disorders
  carpal tunnel syndrome 855–856
  Charcot joint 856–857
  cheiroarthropathy 853–854
  Dupuytren's contracture 855
  fibroproliferative disorders 853–856
  frozen shoulder 854–855
  gout 857–858
  joint disorders 853–858
  limited joint mobility 853–854
  osteoarthritis 858
  rheumatoid arthritis 858
  stenosing tenosynovitis 855
  trigger finger 855
myasthenia gravis 25
My Day tool 364
myocardial abnormalities/infarction 726, 732–742
myocardial energetics 513, 738
myocardial infarction and stroke, three-point major adverse clinical event (MACE) 726
myocardial metabolism 732–733
myosin-and Rab-interacting protein (MyRIP) 88

NaDIA *see* National Diabetes Inpatient Audit
NADPH *see* nicotinamide adenine dinucleotide phosphate
NAFLD *see* non-alcoholic fatty liver disease
nails, skin conditions 841, 844–849
naltrexone 256, 553
NASH *see* non-alcoholic steatohepatitis
nateglinide 492, 496, 505–506
NATHAN trial 664
National Diabetes Data Group (NDDG) 23, 1050
National Diabetes Inpatient Audit (NaDIA) 559, 562–564, 568
National Health and Nutrition Examination Survey, 1988–1994 (NHANES III) 61, 298
National Health Service (NHS)
  bariatric surgery 556–557
  care, aims of 346–347
  cultural/ethnic aspects 990–991
  in-hospital treatment 559, 564, 575
  Low Calorie Diet Programme 256
  oral health 816
  psychosocial aspects 917
  sexual dysfunction 791
  sleep 900
  social aspects 975
national in-hospital treatment guidelines 559, 561–563, 570–571
National Institute for Health and Care Excellence (NICE)
  acute coronary syndromes 335
  adolescents 1020
  bariatric surgery 258, 556–557
  cardiovascular disease 720
  care aims 348
  clinic visits 348
  culture/religion 996
  dietary factors 369, 373–376
  in-hospital treatment 561
  NAFD 831
  obesity 258
  patient education 355
  pregnancy 336–337, 1035, 1040, 1043–1050, 10560
  psychosocial aspects 942, 946, 952
  sexual function 792
National Institutes of Health (NIH) 205, 261, 556–557, 683, 751
natriuresis 523–524, 539
natural killer cells 880
Nauru 65
nausea 602, 605, 796, 802–807
NCD *see* non-communicable diseases
NDDG *see* National Diabetes Data Group
neck infections 218, 313, 884–885
necrobiosis lipoidica 838–839, 842–844
necrotizing fasciitis 333, 845, 878, 892–894
NEED program 363
negative pressure, wound therapy 778
neonatal care 1049
neonatal complications 1037–1040, 1061
neonatal diabetes 158, 167, 283–286, 417, 1002
neonatal hypoglycaemia 1040
neoplasia *see* cancer
neovascularization 632–633
nephropathy 615–626, 640–654
  see also kidney disease
  ACE inhibitors 648–649
  albuminuria 640–652
  antihypertensive agents 648–650
  aspirin 640, 650
  blood glucose 640, 645–652
  blood pressure 640–652
  cardiovascular disease 640–652, 713–716, 718
  care organization 652
  classification 641
  creatinine 640–642, 645–650
  definitions 640–641
  dialysis 640, 648–651
  dietary factors 640–641, 645–646, 649–652
  endothelin receptor antagonists 650
  estimated GFR 640–651
  ethnicity 644
  gastrointestinal tract 797, 802
  genetic factors 644
  glomerular filtration rate 640–651
  GLP-1 RA 648
  glucose management 640–641, 644–652
  histopathology 641–643
  historical perspectives **4**, 18
  hyperfiltration 644
  hyperglycaemia 643
  hypertension 700–704, 707–710
  insulin therapy 650–651
  investigations 645
  islet cell transplantation 473, 480, 482
  lipids 650
  management 640–652
  metformin 650
  mineralocorticoid receptor antagonists 649
  monitoring 645
  morbidity 640, 648–651
  NAFLD 820, 828–831
  natural history 641–643
  oral glucose lowering drugs 647–651
  pathogenesis 615–626
  pregnancy 1041–1043, 1045–1046
  prevention strategies 640, 645–650
  protein ingestion *643*, 649–650
  referral recommendations 651–652
  renin–angiotensin system 640, 642, 646–649, 652
  risk factors 644–645
  screening 640–641
  SGLT-2 inhibitors 640, 644–651
  smoking 650
  sodium intake 649
  transplantation 640, 646, 648–651
  Type 1 diabetes 640–652
  Type 2 diabetes 534–537, 541–548, 640–652
  urine albumin excretion 640–645, 648–649
  weight loss 650
  whole pancreas transplantation 473, 480, 482
  young people 642
nerve conduction 661
nervous system
  complications 615–616, 620, 626, 655–678
  insulin secretion/islet function 84, 89, 93–96
Netherlands 63, 750, 1145
Nettleship, Edward 8
neural activation 579–588
neural control, insulin secretion 93–96
neural regulation 100
neuroglycopenia 579
neurological sequelae 596
neuromodulation 667
neurons 128–139
neuropathy 33, 615–616, 620–626, 655–678, 790
  acupuncture 668
  acute pain 658
  amputations 655–658
  autonomic 655–658, 661–664, 669–674
  autonomic reflex testing 669–670
  biopsies 661–662
  body weight 655–658, 664, 670, 673
  cardiovascular disease 615–616, 622–626, 655–656, 659, 669–671
  care aims 350–351
  central nervous system 659
  children 1016
  classification 655
  clinical presentation 336, 656–659
  colonic dysfunction 673
  combination therapies 667
  corneal confocal microscopy 662–663
  diabetes classification 22
  diagnosis 22, 660–663
  diarrhoea 672–673
  dietary factors 664
  electrical spinal cord stimulation 668
  epidemiology 655–656
  focal/multifocal 655–663, 670
  foot disease 655–664, 667–677, 771–778
  FREMS technique 668

neuropathy (*cont'd*)
gallbladder dysfunction 671
gastrointestinal tract 671–673, 797–806
gastroparesis 671–672
global burden of diabetes 33
gustatory sweating 674
historical perspectives **4**, 8
hyperlipidaemia 655–656, 670, 673
hypertension 655–656, 670–674
infections 878–881, 888–894
intensive therapies 664
islet cell transplantation 473, 480, 482
lifestyle factors 664
lipids 655–656, 670, 673
low-intensity laser therapy 668
management 655–658, 664–674
nerve conduction 661
neuromodulation 667
non-invasive neuromodulation 667
obesity 655–656, 664, 670, 673
oesophageal dysfunction 671
optical coherence tomography 663
pain 655–674, 772, 947, 1016
pathogenesis 615–616, 620, 626, 659–660, 664–665
PENS technique 668
persistent symmetrical polyneuropathies 655–669
pre-diabetes 655, 659–660
pregnancy 1043
quality of life 655, 666–671
quantitative sensory testing 660–661
rapidly reversible 655–656
sexual dysfunction 673–674, 780–783, 790
skin biopsies 661–662
skin conditions 661–662, 848
sleep 655–657, 660, 667–670, 897, 899, 901
sudoscan 663
symptom assessments 660
TENS devices 667–668
topical medications 667
Type 1 diabetes 656, 659–666, 669–673
Type 2 diabetes 656–660, 664–665, 669–673
ulceration 655–663, 667–671
urogenital system 673–674
vibration perception threshold 661
weight loss 664
whole pancreas transplantation 473, 480, 482
neuropeptides 84, 89, 93–96
neuroprotective effects of GLP-1 524
neuropsychologists 929
neurotransmitters 84–85, 88–95, 144
neutral protamine Hagedorn (NPH) insulin 434–436, 439–441, 1006–1008, 1046
neutrophils 878–882, 888, 891
New Zealand 29–31, 44–46, 65, 1053–1054
next-generation sequencing 157–160, 167, 261
NHANES III *see* National Health and Nutrition Examination Survey
NHS *see* National Health Service
NICE *see* National Institute for Health and Care Excellence
nicotinamide adenine dinucleotide phosphate (NADPH) 620, 681–685, 691–693
nicotinic acid (niacin) 718
NIH *see* National Institutes of Health
nitric oxide (NO) 745, 748, 780–788, 967
N-methyl D-aspartate (NMDA) antagonists 931
NNRTI *see* non-nucleoside reverse transcriptase inhibitors
nocturia 331–332, 513, 898, 1001
nocturnal hypoglycaemia 596
nodular glomerulosclerosis *13*
non-alcoholic fatty liver disease (NAFLD) 720–721, 820–837
aetiology 825–827
age-related incidence 820, 823–826, 831
arrhythmias 829–830
bariatric surgery 820, 832
biopsies 821–824
cancers 820, 823–835
cardiac diseases 829–830
cardiovascular disease 720–721, 820–821, 825, 828–830, 833–834
chronic kidney disease 820, 828–831
cirrhosis 820–835
definitions 821
diagnosis 821–825
dietary factors 832, 834–835
drug therapies 820, 825, 832–835
dyslipidaemia 820, 825–831
epidemiology 821
ethnicity 820–821, 825–828
genetics 820, 825–828
GLP-1 RAs 834
glycated haemoglobin 820, 822, 825, 829
hepatocellular carcinoma 820, 823–835
hepatocellular injury 820–823, 826–828
insulin action 111, 121–123
insulin resistance 242–247, 820–822, 825–832, 835
kidney disease 820, 828–831
lifestyle factors 832
lipids 821–835
liver fat (steatosis) 821–828, 832–834
liver fibrosis 820–835
macrovesicular steatosis 820–821
management 820, 824–825, 829–835
metabolic factors 820–835
metformin 833
morbidity 820, 830, 834
mortality 820, 830, 834
multisystem diseases 828–831
nephropathy 820, 828–831
novel therapies 835
obesity 197, 250–254, 820–835
obeticholic acid 820, 835
pathogenesis 825–827
pioglitazone 820, 825, 833–834
sex-related incidence 820, 825, 828, 831
steatosis 821–828, 832–834
Type 2 diabetes 242–247, 250–254, 820–835
non-alcoholic steatohepatitis (NASH) 534–537, 541–542, 546–548, 820–822, 825–835
non-classical diabetic nephropathy 642–643, 648–649
non-coding RNAs 192
non-communicable diseases (NCD) 1108–1117
non-digestible dietary starch fermentation 262
non-healing ulcers 755
non-Hodgkin's lymphoma 34
non-insulin-dependent diabetes mellitus *see* Type 2 diabetes
non-insulin parenteral therapies
adverse-effects 520, 525–529
amylins 520, 529–530
body weight 520–530
cardiovascular outcome trials 520, 523–530
GIP 521–522, 529–530
GLP-1 520–530
GLP-1 RA 520–521, 523–530
GLP-2 521–522
management 520–533
peptides 520–530
proglucagon distribution 522–523
Type 1 diabetes 520, 529–530
Type 2 diabetes 520–530
non-invasive neuromodulation 667
non-nucleoside reverse transcriptase inhibitors (NNRTI) 151
non-nutrient regulation 92–96
non-nutritive sweeteners 373
non pharmalogical hypertension treatments 706
non-randomized Type 2 diabetes studies 390
non-steroidal anti-inflammatory drugs (NSAID) 707, 853–854, 858
non-viral vectors 1144, 1148–1150
Noorden, Carl von 8–9
Nordic Countries 62–63
see also individual countries
norepinephrine 84, 93–94, 312–313, 581, 584, 666–667, 966
normal motor functions 797–798
normal physiology
body weight 142–154
brain 128–139
glucagon 99–108
glucose homeostasis 128–141
glucose metabolism 77–83
insulin action 111–127
insulin secretion/islet function 84–98
islet regulation 99–108
metabolic regulation 99–108
normoglycaemia 23, 26, 70, 137–139
normokalaemia 295, 299
North Africa 29–30, 55, 59, 64–65, **68–69**
North America 29–30, 61–62
Northwestern Ontario 977–978
Norway 43–46, 50–51
NovoPen® devices 460
Nox isoforms 691–692
NPH *see* neutral protamine Hagedorn insulin
NSAID *see* non-steroidal anti-inflammatory drugs
nucleoside reverse transcriptase inhibitors (NRTI) 151, 295, 299
nurses, multidisciplinary teams 1104
Nurses' Health Study 56–57
nutrients 84, 87–96
insulin action 111–112, 116–124
insulin secretion 84, 87–96
metabolism 89–92, 1164

oral glucose lowering drugs 492–493, 499, 507–510, 514–515
Type 2 diabetes 1155–1156
nutrition 368–381
see also dietary factors
adolescents 1019–1020, 1024
bariatric surgery 556
care aims 347
children 999–1001, 1005, 1008
end-of-life care 1091
gastrointestinal tract 796–797, 802, 806–807
heritability aspects 192
insulin resistance 246–247
older patients 1082
transition to adulthood 1019–1020, 1024
Type 1 diabetes 50–51
Type 2 diabetes 246–247

OAGB *see* one anastomosis gastric bypass
obesity 142–154, 197–201, 250–260, 551–557
adipose tissue 197–199, 250–254
Albright hereditary osteodystrophy 198
antidepressants 151
anti-obesity medications 150–151, 256–258, 517, 552–554, 1164
antipsychotic drugs 150–151
antiretroviral therapy 151
appetite-regulation hormones 142–146, 149–151
bariatric surgery 250, 255, 258
BDNF signals, genetics 198
behavioural factors 142–152
β-cell function 250, 252–255
biomarkers/precision medicine 414, 417, 422
blood pressure 250, 254–256
body mass index 197, 201, 250–258
carbohydrate metabolism 250, 255
cardiorespiratory function 250, 255
cardiovascular disease 551–555
children 197–201, 250, 252
ciliary disorders 198
circadian patterns 149–150
comorbidities 142, 147–148, 150–151, 547
definitions 250–251
developmental delay 198–200
diabetics syndemic 252
dietary composition 150
dietary factors 142–152, 250, 254–258, 368–369, 371, 375–376
discrimination 151–152
energy homeostasis/restriction 142–152, 255–256, 551–552
environmental risk factors 142, 147–152
epigenetic influences 147–152
evolutionary perspectives 147
familial clustering 197–198
food 142–152, 197–199
gastrointestinal tract 198
genetics 142, 148–152, 197–201, 250–254, 1150
gestational diabetes mellitus 1060–1061
GIP 250, 256–257
GLP-1 250, 256–258
GLP-RA 250, 256–258, 520–530
glucose homeostasis 128, 131–137
gut hormones 145–146
heart failure 734
hedonic pathways 145
heritability 250, 252
hypothalamus 144, 147–148, 197–201
infections 878–883, 886–887
insulin resistance 250–258, 1150
internalization 151
leptins 199–200
life expectancy 142, 151
lipids 250–251, 254–256
low-calorie/energy diets 255–256, 551–552
management 142–154, 250–260, 551–557
Mendelian disorders 197–198
mental disorders 933–937, 944–946, 949–952
metabolic dysfunction 250–256
monogenic 147–148
morbidity 142, 147–148, 150–151, 547
NAFLD 197, 250–253, 820–835
neuropathy 655–656, 664, 670, 673
oral glucose lowering drugs 492–495, 499–501, 507–510, 513, 517–518
pathogenesis 197–202, 250–260
pathophysiology 252–254
phenotypes 250–251
physical activity 197
policy effects 152
polygenic susceptibility 148
Prader-Willi syndrome 198
pregnancy 1034–1039, 1042–1050, 1056–1066
psychological support 551–552
psychosocial aspects 933–952
randomized controlled trials 551–553
rare variant genes 197, 200–201
regulation 142–152, 198
Roux-en-Y gastric bypass 146–147, 554–556
sleep patterns 149–150
social factors 142–143, 149–152, 933–952
Src-homology-2 B-adaptor protein-1 198
stigma factors 142, 149, 151–152
stroke 748
subcutaneous fat 250, 253–254
toxins 150–151
tropomyosin-related kinase B 198
twin cycle model 250, 254
Type 1 diabetes 258
Type 2 diabetes 142, 147, 150–151, 250–258
epidemiology 56–59, 62–70
future drug treatments 1164
glucose homeostasis 136
metabolic surgery 551–557
treatment in clinical practice 534–549
very low-calorie/energy diets 255–256, 551–552
visceral fat accumulation 250–254
waist circumference 250–252, 256
obeticholic acid 820, 835
obsessive compulsive disorder 939–940
obstetric surveillance 1034–1035, 1047–1048
obstructive sleep apnoea (OSA) 898–902
occlusion of capillaries 629–631, 637
occupational therapists 927–928
OCT *see* optical coherence tomography
octreotide 306
ocular fundus 629, 631, 634–635
oesophageal dysfunction 671
oesophageal dysmotility 671, 802
offloading 774, 776–777, 1102
OGTT *see* oral glucose tolerance test
older patients 1072–1084
Alzheimer's dementia 1079
care homes 1072–1074, 1077–1078, 1081–1082
cognitive function 1072–1082
comorbidity 1072–1082
dementia 1072–1082
depression 1072, 1074, 1079, 1082
diagnosis criteria 1075
dyslipidaemia 1075, 1077
education 1082
epidemiology 1072–1073
frailty 1072–1083
geriatric syndromes 1072–1078, 1081–1082
glycaemic levels 1072–1082
holistic approaches 1082
hyperglycaemia 1074–1081
hypertension 1075–1077
hypoglycaemia 1072–1082
insulin resistance 1073, 1075–1076, 1079, 1082
insulin secretion 1073, 1082
life expectancy 1072, 1075–1077, 1080–1083
lifestyle factors 1075–1076
management 1075–1082
multidisciplinary teams 1103
multiple interventions 1075, 1077–1078
nutrition 1082
pathogenesis 1073
phenotype of diabetes 1073–1075
physical activity 1072–1074, 1078–1082
polypharmacy 1081
quality of life 1072, 1076–1082
recognition aspects 1078–1080
reverse metabolism 1075, 1078
screening 1072, 1074, 1080–1082
self-management 1072, 1079–1080
omega-3 fatty acids 374, 718–719, 834–835
once-daily injections 431, 439, 441
onco-diabetology 867, 875–876
one anastomosis gastric bypass (OAGB) 555–556
one-step universal pregnancy test 1056–1057
ongoing diabetes care 347–352, 354–355, 363–365
online health information 410, 902, 915, 938
ONTARGET study 690, 695, 708, 1076
open surgical revascularization 759–760
operating theatres 573
Opie, Eugene L. 13
opioids 666–667, 801
optical coherence tomography (OCT) 635–636, *638*, 663
oral anti-diabetic agents
see also individual preparations
biomarkers/precision medicine 414, 417–422, 426
body weight 553–554
brain control 138–139

oral anti-diabetic agents (*cont'd*)
cancers 867–868, 871–876
dementia 931
glucose homeostasis 138–139
heart failure 741–742
historical perspectives **15**, 16–17
pregnancy 1034, 1038, 1047–1049, 1052, 1059, 1064–1066
skin conditions 849–850
oral contraceptives 295, 297–298
oral glucose lowering drugs 492–519
see also individual preparations
adverse-effects 501, 504–505, 508, 514, 516–517
algorithms 494–498
β-cell function 492–494, 501–504, 508–511
body weight 492–494, 497–501, 504–518
cardiovascular disease 492–518
complications 492–495
contraindications 500, 503–504, 507–508, 513, 515–517
dietary factors 492–496, 501, 516–518
efficacy 500–501, 504, 508, 511, 513–514, 516–517
exercise 492–496, 501, 518
fixed-dose combinations 517
general features **497**
guidelines 494–498
hormones 492–493, 496, 503–504, 508–515
hyperglycaemia 348, 492–518
indications 500, 503–504, 507–508, 513, 515–517
insulin resistance 492–496, 499, 504–507, 511–518
interactions **498**
lifestyle factors 492–496, 500–501, 504–507, 510–513, 517–518
modes of action **496**, 499–503, 506–507, 509, 511–517
nephropathy 647–651
nutrients 492–493, 499, 507–510, 514–515
obesity 492–495, 499–501, 507–510, 513, 517–518
pathophysiology 493–494
pharmacokinetics 500, 503, 507, 509–510, 513, 515–517
prandial insulin releasers 492, **496–498**, 505–506
renal risks 492, 494–501, 504–514, 518
travel 970
Type 2 diabetes 492–518, 534–550
oral glucose tolerance test (OGTT) 23–24, 27, 61
oral health 810–819
cancer 810, 817
candidal infection 810, 816
caries 810, 816–818
clinical management 810–818
gingivitis 810–816, 818
guidelines 817–818
healthcare teams 817–818
hyposalivation 810, 816–818
pathogenesis 814–815
periodontitis 810–818
Type 1 diabetes 813, 816–818
Type 2 diabetes 813–818
organism-specific infections 881–882
organoids, stem-cell therapy 1143
ORIGIN trial 70, 541–542, 719, 726, 742, 874
orlistat 68, 70, 256, 553
orthostatic hypotension 671
OSA *see* obstructive sleep apnoea
osmotic diuresis 330–333, 603–607
osmotic symptoms 336
osteoarthritis 657, 858
osteomyelitis 777
osteoporosis 793, 859–863
osteoprotegerin 681, 692
otelixizumab 1128–1129
otitis externa 845, 878, 884
Ottawa Charter 358
outpatient insulin therapy, s 441–442
ovarian hyperandrogenism 289
overnutrition 57, 246, 1060–1063
overt diabetes 295–302, 1035–1036, 1049, 1053–1055, 1058, 1062
overt motor neuropathy 657–658
Oxford Vascular Study 745
oxidative stress 681–685, 688–692, 799–800
oxyntomodulin 143–144

P13K *see* phosphatidylinositol 3-kinase
Pacific Islands 29–31, 55, 65–67
Package of Essential Noncommunicable Disease Interventions (PEN) 1116
paediatric ambulatory care 1004–1006
pain
neuropathy 655–674, 772, 947, 1016
peripheral vascular disease 755
PAK 484
Pakistan 36, 47, 64, 975, 988–991, 1085
palliative care/medicine 1086–1089, 1093
see also end-of-life care
PALY *see* productivity-adjusted life years
PAM genes 157, 167
pancreas
artificial 453, 455, 457, 461, 464–465, 918
glucose homeostasis 128–139
pancreas donor risk index (PDRI) 485–486
pancreatic adverse events 528
pancreatic amyloidosis 222–223
pancreatic carcinomas 319–320, 324–327
pancreatic duodenal homeobox 1 (Pdx1) 100, 157, 167
pancreatic exocrine dysfunction 288
pancreatic insulin 523
pancreatic islets
see also islet cells
adenomas 304–315
iron deposition 319, 325–326
of Langerhans 77–78, 84, *89*, 96, 227
transplantation 473–491
pancreatic lineage 1139
pancreatic neoplasia 326
pancreatic polypeptides (PP) 78, 93
pancreatitis 319–329
acute 319–320
calcific 319–324
carcinomas 319–320, 324–327
chronic 319–328
clinical presentation 281–282, 286–288, 321, 325, 331–332
cystic fibrosis 319–320, 327–328, 1036
diabetes in 323, 326–327
diagnosis 321
drug-induced diabetes 295, 299
epidemiology 319
fibrocalculous pancreatic diabetes 319–324
haemochromatosis 319–320, 324–326
hyperglycaemia 319–320, 327
insulin 319–328
investigations 321–322
management 319–320, 323–328
surgical management 319–320, 326–327
tropical calcific 319, 323–324
Type 1 diabetes 222–223
weight loss 319, 323–328
pancreatobiliary secretions 797–798
PARADIGM-HF trial 695, 739
paraganglioma 304, 312–314
Paraguay 44
parasympathetic nervous system (PNS) 129–130
parathyroid hormones 304, 313, 316–317
PARD *see* precision absolute relative deviation
parenteral non-insulin therapies 520–533
parent-of-origin effects 157, 160, 191–192
parents
adolescents/transition to adulthood 1019–1026, 1030–1031
psychological reactions 907, 909–915, 918–919, 970, 1005, 1012–1013, 1019
partial lipodystrophy 275, 278, 288–291
participant-oriented principles 354–365
Parving, Hans-Henrik 18
patch pumps 459, 468–470
patient-centred care 343–352
patient education
behavioural factors 358–361, 908, 917–918
biomedical aspects 361–362
care aims 347
change-based relationships 358, 363–364
competency 355–356
counselling 359–361
cultural aspects 362–364
dialogue 356–358
empowerment 354–367
evaluation 364–365
family-based groups 354–355, 362–365
foot disease 771, 774–775
healthcare involvement 354–365
healthcare teams 356–365
language 361
lifestyle factors 354
mindsets 361, **362**
modalities 355
older patients 1082
ongoing care 354–355, 363–365
outcome improvements 361–362
participant-oriented principles 354–365
physical activity 354–356, 364
pregnancy 1034–1038, 1044, 1049, 1058–1060
programme theory 364–365
psychological issues 354–356, 359–365
psychosocial aspects 908, 917–918
self-management 354–365
social contexts 362
training aspects 354, 357, 376
values, competencies, and tools 355–356
Patient Health Question-9 (PHQ-9) 938

patient involvement in care planning and development 352
Patient-Reported Outcomes Information System (PROMIS) 902
patient safety/satisfaction in hospital 562–564
Paulescu, Nicolas 9, 11, 432
Pavy, Frederick 8
PCOS *see* polycystic ovarian syndrome
PCR *see* polymerase chain reaction
PCSK1 *see* prohormone convertase 1
PCSK9 *see* proprotein convertase subtilisin kexin-9 inhibitors
PD1 *see* programmed death 1 receptors
PDE5 *see* phosphodiesterase 5 inhibitors
PDRI *see* pancreas donor risk index
Pdx1 *see* pancreatic duodenal homeobox 1
Pedersen, Jørgen 18–19
PedsQL tool 913
pegvisomant 307–308
PEN *see* Package of Essential Noncommunicable Disease Interventions
pen devices 435, 441–446, 459–460, 468
penile prostheses 780, 787–788
pentamidine 299–300
peptides
  see also individual peptides
  non-insulin parenteral therapies 520–530
  normoglycaemia restoration 137–138
  peptide mixtures 1158–1160
  peptide processing 101
  Type 2 diabetes 1154–1164
peptide YY 3-36 143–144
perceived glucose deficiency 135–137
percutaneous electrical nerve stimulation 668
percutaneous transluminal angioplasty 758–759
perforating skin disorders 847
perinatal factors 50–51, 1052
periodontitis 338, 810–818, 885
perioperative in-hospital treatments 570–572
peripheral arterial disease 755–767, 771–776, 878–881, 893
peripheral neuropathy 33, 615–616, 620–626, 655–678, 790
peripheral sympathetic autonomic neuropathy 772
peripheral vascular disease 755–767
  amputations 755, 757–762
  aneurysms 755, 762–765
  arm ischaemia 762
  asymptomatic stage 755
  atherosclerosis 755–767
  blood pressure 755–757, 762–763
  carotid artery disease 755, 765–767
  claudication 755
  diagnosis 756–757, 760–761, 763, 765
  foot disease 771, 773–776
  incidence 755–756
  infections 878–881, 893
  interventions 758–760
  lower limb symptoms 757
  management 757–761, 763–766
  mesenteric artery occlusive disease 761–762
  non-healing ulcers 755
  open surgical revascularization 759–760
  pathophysiology 755, 760, 762–763
  percutaneous transluminal angioplasty 758–759
  prevention strategies 761
  prognosis 757, 761, 763, 765
  renal artery obstruction 761–762
  rest pain 755
  screening 764
  stenting 766–767
  surgical management 758–760
  symptoms 760, 762–763
  technical considerations 766
  thrombosis 760–761
  ulceration 755
periphery retinopathy 629–637
peri-procedural care 473, 485–488
peritoneal space 436
periungual telangiectasia 838–839, 843–844
permanent neonatal diabetes mellitus (PNDM) 283–286
permeable intestinal mucosa 261–264, 268
pernicious anaemia 25
peroxisome proliferator-activated receptor (PPAR) γ-coactivator 1a (PGC1a) 833–834
  future drug treatments 1154–1155, 1161–1163
  insulin resistance 242
  monogenic diabetes 275, *277*, 291–292
  Type 2 diabetes genetics 157, 167, 193
peroxisome proliferator-activated receptors (PPAR) 157, 167, 193, 242, 1154–1155, 1161–1163
persistent symmetrical polyneuropathies 655–669
personalized insulin therapy, selection techniques 439–441
personal travel identification 967
Peru 110
PGC1A *see* peroxisome proliferator-activated receptor (PPAR) γ-coactivator 1a
PH *see* pleckstrin homology
phaeochromocytoma 312–313
phagocytosis infections 878–882, 891
pharmacists 1104
pharmacogenetics 414–416, 424
pharmacogenomics 1164–1165
pharmacokinetics 500, 503, 507–510, 513–517, **524**
pH capsule 805
phenformin 17
phenotypes
  disorders and atypical 216–224
  obesity 250–251
  older patients 1073–1075
phentermine 256, 553
PHIP *see* pleckstrin homology domain–interacting proteins
phosphates 607
phosphatidylinositol 3-kinase (P13K) 115–116
phosphodiesterase 5 (PDE5) inhibitors 780–781, 784–786, 791
phospholipase C (PLC) 89
phosphotyrosine binding domains 114
photocoagulation 629, 634–638, 958–959, 1045
phycomyces infections 846
physical activity *see* exercise
physical changes, adolescents 1019–1031
physical disabilities 34–35
physical fitness 382–384, 388, 390, 393, 397
physiotherapists 927
Pickup, John 16
pigmented papillomatous 838
pilgrimage, cultural/religion aspects 994–995
pilot licenses 960–961
Pima Indians 30, 56, 61, 159, 228–229, 643, 700, 1062–1063
pioglitazone 493, 496, 506–508
  cancers 873–874
  ischaemic heart disease 726
  NAFLD 820, 825, 833–834
  Type 2 diabetes 534–537, 541–542, 546–548
PIONEER-6 trial 527, 543
Pittsburgh Insulin-Dependent Diabetes Mellitus (IDDM) 383–384, 389
Pittsburgh Sleep Quality Index 897, 902
PKA *see* protein kinase A
placental growth hormones 1035
planned behaviour theory 360
plantar callus 774
plantar fasciitis 657
plasma glucose 23, 129, 133–138, 579–597
plasma membrane *sn*-1,2-diacylglycerol content 238
plasma protein ketoamines 408
platelet hyperreactivity 748
PLC *see* phospholipase C
pleckstrin homology domain–interacting proteins (PHIP) 200–201
pleckstrin homology (PH) 114, 200–201
pluripotent stem cells (PSC) 1137–1140
PNDM *see* permanent neonatal diabetes mellitus
Pneumocystis jirovecii pneumonia 299–300
podiatry 771
Poincaré plot of system stability 452
point-of-care devices 407, 409
Poland 43, 63
POLD1 gene 291
polycystic ovarian syndrome (PCOS) 304, 314, 316–317
polydipsia 330–333, 343, 346–347, 999, 1001, 1004
polygenic susceptibility, obesity 148
polyglandular syndromes 317
polymerase chain reaction (PCR) test 49, 52
polymorphisms 615, 619, 623–624
Polynesian populations 65
polyneuropathies 655–669
polyol pathways 620
polypeptide hormones 84–86, 143–144
polypeptide YY (PYY) secretion 266–267
polypharmacy 922, 931, 1081
polysaccharides *80*
polyunsaturated fats (PUFA) 373–374
polyuria 330–333, 343, 346–347, 999, 1001, 1004
POMC *see* proopiomelanocortin
popliteal aneurysm 760
porcine insulin 16, 432
portal thrombosis 487
portion size 348, 1008
Portugal 19–20, 941
post-exercise glucose management 399–400

postinsulin era 11–12
postmenopausal women 295, 298
postnatal aspects 50–51, 1034–1036, 1059–1060, 1063–1066
postoperative treatments 570, 573–574
postpartum management 1049, 1059–1060
post-prandial glucose levels 1044
post-prandial hyperglycaemia 444–446, 449–454, 457
post-transcriptional regulation 119
post-traumatic stress disorder (PTSD) 909, 939–941
potassium 607, 1003
potassium channels 90–92
PPAR *see* peroxisome proliferator-activated receptors
P-PASS *see* pre-procurement pancreas allocation suitability score
practice nurses 1104
Prader-Willi syndrome 198
pramlintide 530
PRAMS *see* Pregnancy Risk Assessment Monitoring System
prandial insulin releasers 492, **496–498**, 505–506
precision absolute relative deviation (PARD) 448–449
precision medicine 414–428
  ACE inhibitors 414–415, 422–423
  angiotensin receptor blockers 422–423
  biomarkers 414–428
  blood glucose 414, 417–421
  blood pressure 414–416, 418, 421–423
  cardiovascular disease 414–418, 422–426
  cholesterol 414, 423–425
  clinical practice 425–426, 547–548
  complications 414, 418, 423
  dipeptidyl peptidase-4 inhibitors 420
  genetics 414–426
  GLP-RA 420–421
  glycaemic management 414–420, 425–426
  glycated haemoglobin 415, 417–422, 425
  hypercholesterolemia 414, 423–425
  hyperglycaemia 414, 417–419
  implementation 425–426
  kidney diseases 414–426
  lipids 423–425
  metformin 418–420
  MODY 417–418
  monogenic diabetes 414–418, 426
  neonatal diabetes 417
  oral anti-diabetic drugs 414, 417–422, 426
  pathophysiology 414–417, 426
  pharmacogenetics 414–416, 424
  proteins 414–426
  research directions 425–426
  SGLT-2 inhibitors 421–422
  sulfonylurea derivatives 420
  Type 1 diabetes 414, 418, 423, 426
  Type 2 diabetes 414–426, 547–548
pre-diabetes
  classification and diagnosis 23–24
  neuropathy 655, 659–660
  pregnancy 1034, 1055–1056, 1059–1063
  stroke 747–748
  Type 1 diabetes 1128, 1130
  Type 2 diabetes 56, 63–64, 67
pre-eclampsia 1037–1039, 1042–1045, 1048, 1051–1052, 1056, 1059–1063
pregnancy 1034–1071
  see also fetus; gestational diabetes mellitus
  accelerated fetal growth 1039–1040
  adolescents 1027
  adverse outcomes 1037–1040
  anti-diabetic oral agents 1034, 1038, 1047–1049, 1052, 1059, 1064–1066
  antihypertensive agents 1043
  autoimmune disease 1046
  bariatric surgery 1043–1044
  blood glucose 1034–1040, 1044–1049, 1056–1062
  body weight 1034–1043, 1046–1066
  breastfeeding 1049, 1065
  cardiovascular risk factors 1034–1035, 1047–1063
  classification 23, 25–27, 1036
  clinical presentation f 330, 336–337
  congenital malformation 1034, 1037–1039, 1042–1044
  continuous glucose monitoring 1035, 1044–1045
  contraceptives 295–298, 780, 791–792, 1049
  delivery and labour 1048–1049
  diabetic ketoacidosis 1036–1037, 1041
  dietary factors 368, 376, 1058, 1065–1066
  drug cessation 1046
  education 1034–1038, 1044, 1049, 1058–1060
  epidemiology 1035
  fasting glucose 1034, 1050–1060
  fetal adverse outcomes 1034–1044
  fungal infections 336
  glycaemic management **25**, 27, 1034–1066
  glycated haemoglobin 1034–1041, 1044–1047, 1053–1060
  historical perspectives 18–20
  HNF4A genes 282–283
  hyperglycaemia **25**, 27, 1034–1042, 1045–1063
  hypertension 1041–1043, 1045–1046
  hypoglycaemia 1034, 1037–1051, 1056, 1059–1061
  insulin sensitivity 1035, 1049, 1065
  insulin therapy 1034–1036, 1045–1049, 1058–1059, 1062
  ischaemic heart disease 1043
  kidney disease 336–337
  labour 1048–1049
  lifestyle factors 1058, 1063–1066
  long-term outcomes 1061–1063
  malformations 1034, 1037–1039, 1042–1044, 1052–1055, 1061
  management of diabetes 1044–1045
  metformin 1034, 1038, 1047–1049, 1052, 1059, 1064–1066
  miscarriage 1038–1039
  MODY 280–286
  monitoring diabetes 412
  monogenic diabetes 1036
  mortality 1034–1043, 1047–1060
  multidisciplinary care 1034, 1037, 1043–1044, 1102
  neonatal care 1049
  neonatal complications 1037–1040, 1061
  neonatal hypoglycaemia 1040
  nephropathy 1041–1043, 1045–1046
  neuropathy 1043
  obesity 1034–1039, 1042–1050, 1056–1066
  obstetric surveillance 1034–1035, 1047–1048
  osmotic symptoms 336
  overt diabetes 1035–1036, 1049, 1053–1055, 1058, 1062
  pathophysiology 1035–1036
  pharmacology 1058–1059, 1065
  physical activity 1065
  physiology 1035–1036
  planning 352, 1034–1049, 1058–1060
  postnatal aspects 1034–1036, 1059–1060, 1063–1066
  postpartum management 1049, 1059–1060
  pre-diabetes 1034, 1055–1056, 1059–1063
  pre-eclampsia 1037–1039, 1042–1045, 1048, 1051–1052, 1056, 1059–1063
  pre-pregnancy care/services 466, 1034, 1037–1053, 1059–1065
  probiotics 1066
  renal transplantation 1043
  retinopathy 1041, 1045
  risk engine screening method 1057–1058
  risk factors 1037–1040
  screening 1056–1058
  selective screening 1057–1058
  shoulder dystocia 1040
  sick-day management 1047
  stillbirth 1038–1039
  sulfonylureas 1059
  transition to adulthood 1027
  Type 1 diabetes 49–51, 1034–1049, 1058–1063
  Type 2 diabetes 55–58, 64, 70–71, 1034–1049, 1054–1066
  universal screening 1056–1058
Pregnancy Risk Assessment Monitoring System (PRAMS) 297
premix insulins 440–441
preoperative assessments 571
pre-prandial glucose levels 1044
pre-pregnancy care/services 466, 1034, 1037–1053, 1059–1065
pre-procurement pancreas allocation suitability score (P-PASS) 485–487
pre-proinsulin genes 1148–1149
pre-symptomatic molecular testing 279
Prevotella 261, 265
primary care
  elective surgery 571
  mental disorders 933–939, 942
  multidisciplinary teams 1097–1105
  sexual dysfunction 788
  stroke 749–750
  upskilling 1098
primary hyperaldosteronism 316
primary hyperinsulinaemia 316–317
primary hyperparathyroidism 316
Primrose syndrome 288
prison 956, 962
PROACT II trial 750
PROACTIVE study 541–542, 719, 726
probiotics 1066
processing speed 922–924, 927

productivity-adjusted life years (PALY) 36–37
professional CGM 446
progeroid features 291
proglucagon distribution 101, 522–523
programmed death 1 (PD1) receptors 216
programme theory 364–365
prohormone convertase 1 (PCSK1) 199
proinsulin biosynthesis 86–87
proliferative diabetic retinopathy 335–336, 629–638, 956–959, 962–965, 1015–1016
PROMIS *see* Patient-Reported Outcomes Information System
proopiomelanocortin (POMC) 131, 147, 199–201
proprotein convertase subtilisin kexin-9 (PCSK9) inhibitors 717
prostate cancer 34, 673–674, 868–869
protamine zinc insulin 16
protease inhibitors 295, 299–300
protective variants 190, **191**
protein kinase A (PKA) 102–103
proteins
  biomarkers/precision medicine 414–426
  dietary factors 375
  ingestion 227, 241, *643*, 649–650
  insulin action 121
  metabolism 79
  Type 2 diabetes 157, 160, 167, 190–194
protein tyrosine phosphatase 1B (PTP1B) 1161
proteomics 1164–1165
Prout, William **4**
pruritus 845, 847, 850
PSC *see* pluripotent stem cells
Pseudomonas spp. 845, 848, 884, 890, 893
psoriasis 838, 848–849
psychiatric disorders
  behavioural factors 907–918
  eating disorders 907, 910–915, 942–947, 1029–1030
  mood disorders 910, 913–919
  psychosis 933–934, 947–953
  transition to adulthood 1029–1030
psychoactive drugs 965–968
psychological issues
  behavioural factors 907–919
  body weight 551–552, 933–952
  care aims 343, 346–352
  children 1014–1015
  cognitive dysfunction 922–932
  depression 916–917, 938
  distress reduction 916–917
  education 354–356, 359–365, 908, 917–918
  empowerment 917
  living with diabetes 909–913
  quality of life 916–919
  risk factors for developing diabetes 908–909
  sexual dysfunction 782, 789–791
  sleep 897, 902
  structured training/education 917–918
psychosocial aspects 905–984
  adolescents 907, 910–919, 1019–1031
  alcohol 963–965
  anxiety disorders 907–918, 933–934, 938–942, 945–947
  attention perspectives 922–927
  behavioural factors 907–921
  blood glucose 907, 912–916
  body weight 551–552, 933–952
  children 907–915, 1005–1008, 1014–1015
  cognitive behavioural therapy 908, 916–919
  cognitive dysfunction 922–932
  complications 908–913
  counselling 907, 918–919
  custody 962
  dementia 922–932
  depression 907–918, 933–942, 945, 947–949
  determinants of diabetes 973–984
  diabetic ketoacidosis 907, 911
  discrimination 907, 911–912
  distress 908–919
  driving 956–962
  eating disorders 907, 910–915, 942–947
  education 908, 917–918
  emotional factors 908–918
  employment 961–962
  empowerment 908, 917
  environmental risk 908–909, 914
  executive function 922–930
  family factors 908–919
  family therapy 908, 911, 916–919
  glycaemic control 907–918, 922–926
  group therapy 907, 918–919
  hyperglycaemia 922–926
  hypoglycaemia 907–913, 917–918, 924–926, 930–931
  insulin delivery 918
  insurance 962–963
  language 922–930
  leaving home factors 970–971
  living with diabetes 909–913
  long-term complications 912–913
  management 907–919
  medication factors 922–932
  memory 922–929
  mental disorders 933–955
  mindfulness-based therapies 908, 916–917
  mood aspects 910, 913–919
  obesity 933–937, 944–946, 949–952
  patient education 908, 917–918
  prison 962
  processing speed 922–924, 927
  psychosocial burden 32
  psychosocial support 936, 966
  psychotherapy 908, 916–919
  psychotic disorders 933–934, 947–953
  quality of life 907–919
  recreational drugs 965–967
  retinopathy 907, 912
  screening 922–925, 929–934, 938–939, 942–946, 950–952
  self-management 907–919, 922–932
  sleep 908–910
  stigma factors 907, 912, 917
  stress 908–919
  technology 918
  training approaches 908, 917–918
  transition to adulthood 1019–1031
  travel 967–970
  Type 1 diabetes 907–919, 922–925
  Type 2 diabetes 907–919, 922–927, 930
  visual perception 922–924, 927–930
  web-based CBT 908, 916
  well-being 907–917
psychotherapy 908, 916–919
psychotic disorders 933–934, 947–953
  see also antipsychotic drugs
  definitions 947–948
  diagnosis 947–948
  environmental factors 949
  epidemiology 948
  genetics 949
  management 949–953
  prevention strategies 951–952
  screening 951
  severity of 948–953
PTA 482–485
PTP1B *see* protein tyrosine phosphatase 1B
PTSD *see* post-traumatic stress disorder
puberty 41–42, 45, 49
PUFA *see* polyunsaturated fats
pump devices *see* insulin pumps
pupillary reflexes 669–670
pyruvate carboxylase 238, 245–247
PYY *see* polypeptide YY

Qatar 64–65, 656
quality-adjusted life years (QALY) 36–37
quality factors
  carbohydrates 372–373
  glucose monitoring 445–446
  LMIC care models 1114–1115, **1118**
  sleep 899, 901–902
quality of life
  behavioural factors 907–919
  care aims 343, 347, 351–352
  erectile/sexual dysfunction 783, 790
  gastrointestinal tract 796–797, 801, 807
  insulin delivery 467
  neuropathy 655, 666–671
  older patients 1072, 1076–1082
  psychosocial aspects 907–919
quantitative sensory testing 660–661
quantity factors, carbohydrates 372
questions to ask, care aims 345–346
QUICKI 238
QUIET study 690
quinidine 668
quinine 882
quinolones 300–301, 673, 777, 845, 884, 889–891, 1160

RAAS *see* renin–angiotensin–aldosterone system
race 973–981
  Covid-19 pandemic 992–993, *993*
  culture/ethnicity/religion 987–997
  definitions 987–988
  diabetes related outcomes 990
  dietary factors 992
  discrimination 992
  education, structured 994
  epidemiology 988–990
  exercise and physical activity 992, 994
  fasting and feasting 994
  health inequalities 991
  social determinants of diabetes 973–981
  taboos and barriers 991
  Type 2 diabetes 29–30, 61–64, 67, 987, 990, 997
radiographic contrast media 500, 536

radiotherapy 308
RAGE *see* receptors for AGE
Rahbar, Samuel 17
Ramadan 994–995, **996**
ramipril 70
RANKL osteoprotegerin pathway 621, 692, 814–815, 857, *862*
rapid-acting insulin 431, 433–437, 440–441
rapidly reversible neuropathies 655–665
RAPTOR 117
rare subtypes 283
rare variants 167, 190, 197, 200–201
RAS *see* renin–angiotensin system
rate-of-change information 450–451
rat insulin gene sequences 15
RDA *see* recommended daily allowances
reactive gliosis 128, 132–133
reactive oxygen species 691
readmission aspects 575
real-time glucose levels 446–454, 455, 593
receptors for AGE (RAGE) 619–620, 681–682, 685–689, 696, 814–815
receptor tyrosine kinases 111–115, 121
recognition aspects, older patients 1078–1080
recombinant human insulins 432
recombinant insulin preparations 849
recombinant leptin therapy 199–200
recommended alcohol intake 965
recommended daily allowances (RDA) 373
RECORD trial 506, 541, 741
recovery, in-hospital treatments 573–574
recreational drugs 957, 965–967
recreational travel activities 970
recurrent hypoglycaemia 596
reddening, skin conditions 838, 843–850
reduced ejection fraction therapies 738–741
regenerative endothelial cell repair 687–688
regulatory T (Treg) cells 212, 216–218, 268, 487–488, 1126–1130, 1148
relative insulin excess 579–582, 588, 593–596
religion 987–998
  culture/ethnicity/race 987–997
  definitions 987–988
  discrimination 992
  epidemiology 988–989
  fasting and feasting 994–995, **996**
  pilgrimage 994–995
  ritual impacts 994–995, **996**
  South Asian populations 994
  taboos and barriers 991
remission from Type 2 diabetes 55, 59, 70–71, 254–258, 370–371
renal artery obstruction 761–762
renal artery stenosis 705
renal denervation 695
renal disease
  see also kidney disease
  global burden of diabetes 33–34
  obesity 142, 148
  stem-cell therapy 1142–1143
renal function 523–524, 897, 901
renal glucose filtration 80–81
renal replacement therapy 351, 415, 543–544
renal risks of glucose lowering drugs 492, 494–501, 504–514, 518
renal threshold 330–331
renal transplantation 1043
renin–angiotensin–aldosterone system (RAAS) 681–682, 686–690, 695, 700–702, 707–709
renin–angiotensin system (RAS) 640–642, 646–649, 652, 732–734, 738–740
repaglinide 492, 496, 505–506
resistance training exercises 382, 384–400
respiration (Kussmaul breathing) 333, 602, 605, 999, 1001–1002
respiratory mucosal surface 436–437
respiratory tract infections 885–888
resting metabolic rate 146, 151, 199
restless leg syndrome 897–898
rest pain 755
retinal exudates 633
retinal neovascularization 632–633, 637, 1041
retinal periphery 629–637
retinal photocoagulation 629, 634–638, 958–959, 1045
retinopathy
  aneurysms 629–630, 634–637
  angiography 635–636
  behavioural factors 907, 912
  blindness 629, 633–635
  capillaries 629–631, 637
  central vision 629–630, 633–634, 637
  children 1015–1016
  clinical presentation 333, 335–336, 632–633
  complications 615–621, 629–640
  development 629–633
  diagnosis 635–636
  driving 947–949, 957
  early stages 629–631
  epidemiology 629–630, 633–634
  fluorescein angiography 635–636
  gastrointestinal tract 797, 800, 802
  global burden of diabetes 33
  haemorrhages 629–637
  historical perspectives **4**, 8, 15, 18
  hypertension 700–703, 709–710
  indigenous populations 1101–1102
  intravitreal angiostatic treatment 629, 634, 637–638
  investigations 638
  islet cell transplantation 481–482
  lesions 629–637
  maculopathy 629–631, 633–637
  management 636–638
  microaneurysms 629–630, 634–637
  morphological lesions 629–637
  multidisciplinary teams 1101–1102
  nomenclature 629–630
  OCT scanning 635–636, *638*
  ocular fundus 629, 631, 634–635
  pathogenesis 615–621
  pathophysiology 629–630, 638
  photocoagulation 629, 634–638, 958–959, 1045
  pregnancy 1041, 1045
  prevention strategies 634–636
  psychosocial aspects 907, 912
  retinal photocoagulation 629, 634–638, 958–959, 1045
  screening 629, 633–638, 958–959
  Type 1 diabetes 629, 632
  Type 2 diabetes 629, 634
  vision-threatening 33, 629–635
  whole pancreas transplantation 480
retroviral drugs 151, 299, 878, 883–884
retroviral vectors 1146, 1148–1149
Reuting, Ruth 15
revascularizations
  drug-induced diabetes 299
  foot ulcers 775
  ischaemic heart disease 726–728
  monitoring aspects 406
  peripheral vascular disease 756–763, 767
  risk prevention 1101
  stem cell therapy 1141
  stroke 749, 752
  Type 2 diabetes 542
  vasoactive hormones 690
reversal of Type 2 diabetes 254–258
reverse metabolism in older patients 1075, 1078
REWIND trial 415–416, 527, 542–544, 694, 727, 737, 749
RHEB 116–117, 120
rheumatic disorders 853–866
  bone density 793, 859–863
  carpal tunnel syndrome 855–856
  Charcot joint 856–857
  cheiroarthropathy 853–854
  diffuse idiopathic skeletal hyperostosis 858–859
  Dupuytren's contracture 855
  fibroproliferative disorders 853–856
  fractures 793, 859–863
  frozen shoulder 854–855
  gout 857–858
  joint disorders 853–858
  limited joint mobility 853–854
  musculoskeletal disease 853–863
  osteoarthritis 858
  osteoporosis 793, 859–863
  rheumatoid arthritis 858
  skeletal disease 858–863
  stenosing tenosynovitis 855
  trigger finger 855
rheumatoid arthritis 858
rhinocerebral mucormycosis 878, 884, 891
risk engine screening method 1057–1058
risk factors
  alcohol 963–965
  body weight 551–555
  cancers 867–876
  cardiovascular disease 551–555, 713–730, 1034–1035, 1047–1063, 1097–1104
  children 1015–1016
  dementia 1079
  exercise-related adverse-events 398
  foot disease 771–778
  gestational diabetes mellitus 1054–1055
  heart failure 733–737
  hypoglycaemia 579–597
  insulin resistance 240
  ischaemic heart disease 724–730
  kidney disease 644–645
  nephropathy 644–645
  pregnancy 1037–1040
  sexual dysfunction 780
  stroke 745–748
  Type 1 diabetes 48–52
  Type 2 diabetes 55–71, 240

risk scores 732, 735, 1001
ritual impacts, religion 994–995, **996**
rituximab 1131
RNA transfer 1144–1147
Rochester Diabetic Neuropathy Study 796
rodenticides 50
Rollo, John 4, 6, 8
Roma, Ernesto 19–20
Romania 43, 432
rosiglitazone 541, 873–874
Roux-en-Y gastric bypass (RYGB) 146–147, 554–556
Rowland Universal Dementia Assessment Scale (RUDAS) 923
rubella syndrome 49
rubeosis faciei 844
RUDAS *see* Rowland Universal Dementia Assessment Scale
Ruminococcus 261
Russia 63, 1085
RYGB *see* Roux-en-Y gastric bypass

saccharides *80*, 373
safety
  exercise 398–399
  gene therapy 1144–1150
  GLP-1 RA 528–529
  immunotherapies 1129–1133
  in-hospital treatments 562–563
  Type 1 diabetes 1129–1133
  Type 2 diabetes 534–548, 1165
Saharan Africa 30, 44–45, 59–61
SAID *see* severe autoimmune diabetes
Saint Vincent Declaration 344, 1034
saline therapy 235, 637, 1002–1003, 1011
salivation, 810, 816-818m 338, 810, 816–818
Salmonella spp. 882, 892
salt 375
Sanger, Frederick 14–15
Sardinia 42–44, 46
SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) *see* Covid-19 pandemic
satiety responsiveness 197
satisfaction, in-hospital treatments 563–564
saturated fats 373–374
Saudi Arabia 30, 65, 879
SAVE trial 739
SAVOR-TIMI trial 542, 546, 726, 735, 737, 741
saxagliptin 492, 496, 509–510, 546
Scandinavia 62–63, 643, 716, 810–811, 962
Scandinavian Simvastatin Survival Study 716
schizophrenia 933–934, 940, 947–952
schools, diabetes management 1005–1006
sclerodactyly 841
scleroedema 841
Scott, Ernest 9
screening
  anxiety disorders 942
  autoimmune Type 1 diabetes 212–213
  cancers 867–868, 875–876
  children 999, 1005, 1008, 1012, 1015–1016
  cognitive function 922–925, 929–931
  cost-effectiveness in pregnancy 1058
  depression 938
  foot disease 772–773
  gestational diabetes mellitus 26–27
  hypertension 703–704
  islet autoimmunity 212–213
  mental disorders 933–934, 938–939, 942–946, 950–952
  nephropathy 640–641
  older patients 1072, 1074, 1080–1082
  peripheral vascular disease 764
  pregnancy 1056–1058
  psychosocial aspects 922–925, 929–934, 938–939, 942–946, 950–952
  retinopathy 629, 633–638, 958–959
SD *see* standard deviation
SDG *see* Sustainable Development Goals
SEARCH for Diabetes in Youth Study 33, 46, 62, 277, 333, 1016, 1020, 1027
seasonal variation in Type 1 diabetes 47
secondary care 752–753, 1097–1105
secondary haemochromatosis 326
second generation antipsychotics 295, 297
sedentary lifestyles 55–57, 90, 383–384, 389–390, 397–398
selective screening 1057–1058
selective serotonin reuptake inhibitors (SSRI) 939, 942
self-advocacy 1021–1022, 1029
self-determination theory 360
self-efficacy 354–357, 360–362, 1019–1023, 1026–1031
self-management
  adolescents 1019–1031
  behavioural factors 907–919
  care aims 343–352
  children 999, 1005, 1013–1015
  cognitive function 922–932
  dementia 925–932
  education 354–365, 1098–1099
  foot disease 771, 774–775
  hypoglycaemia 579, 592–593
  in-hospital treatments 563
  multidisciplinary teams 1098–1104
  older patients 1072, 1079–1080
  patient education 354–365
  psychosocial aspects 907–919, 922–932
  sleep 897, 901–902
  transition to adulthood 1019–1031
self-monitoring blood glucose 347–348, 409–411, 592–594
  adolescents 1022–1025
  children 1013–1014
  insulin therapy 437–438, 441–442
  novel technologies 444–452
  pregnancy 1045–1046
  psychosocial aspects 915–916
Self-Regulation Model 358–360
semaglutide 493, 496, 514
  anti-obesity medications 256–257, 553
  parenteral therapies 526–529
  Type 2 diabetes 538–539, 542–543, 546–547
sensor-augmented pump therapy 431, 438, 464, 474, 597
sensor calibration 449
sensorimotor dysfunction 796, 802
sensorimotor polyneuropathy 655–669
  amputations 655–658
  clinical manifestation 655–658
  diagnosis 660–663
  epidemiology 655–656
  foot ulceration 655–663, 667–671
  pain therapies 668–670
  pathogenesis 659–660
  ulceration 655–663, 667–671
sensory loss 480, 656–658, 761, 772
sensory neuropathy 336, 389, 655–669, 772, 800, 881, 891–893
serotonin–norepinephrine reuptake inhibitors 666
Ser/Thr phosphorylation 119–120
serum creatinine 640–642, 645–650
serum osmolality 609–610, 1002–1004
setmelanotide 256
severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) *see* Covid-19 pandemic
severe autoimmune diabetes (SAID) 159
severe insulin-deficient diabetes (SIDD) 159
severe insulin-resistant diabetes (SIRD) 159
severe mental illness *see* psychotic disorders
severity
  diabetic ketoacidosis 603–607
  psychotic disorders 948–953
sex-related incidence
  NAFLD 820, 825, 828, 831
  Type 1 diabetes 41–43, 204
sexual dysfunction 673–674, 780–795
  alcohol 790
  autonomic neuropathy 780–783, 790
  cardiovascular disease 780–786, 790–793
  care aims 352
  clinical approaches 782–784, 789–790
  erectile dysfunction 673–674, 780–790
  female 673–674, 780, 788–793
  genitourinary infections 791
  infections 791
  intracavernosal injection therapy 780, 786, 788
  investigations 783–784, 790
  male 673–674, 780–790
  management 782–788, 791–793
  medication factors 782, 784–787, 791–793
  neuropathy 673–674, 780–783, 790
  nitric oxide 780–788
  pathophysiology 789
  PDE5 inhibitors 780–781, 784–786, 791
  penile prostheses 780, 787–788
  peripheral neuropathy 790
  physiology 780–782, 788–789
  psychological issues 782, 789–791
  quality of life 783, 790
  risk factors 780
  sildenafil 780, 784–786
  smoking 783, 790
  surgical management 780, 787–788
  transurethral alprostadil 780, 787
  vacuum therapy 780, 787
sexual health
  care aims 352
  contraceptives 295–298, 780, 791–792
  hormone replacement therapy 295, 298, 780, 791–793
SFA *see* short-chain fatty acids
SGLT-2 *see* sodium–glucose cotransporter 2 inhibitors
SHEP *see* Systolic Hypertension in the Elderly Program

shin spots, skin conditions 842
short acting GLP-1RAs 525
short-acting insulin therapys 433–435, 437
short-chain fatty acids (SFA) 369–370, 373–374
SHORT syndrome 291
shoulder dystocia 1040
shunt vessels 631–633
sibling relative risks 159
sick-day management 1012–1013, 1047
sickness, employment and diabetes 961–962
SIDD *see* severe insulin-deficient diabetes
signalling cascade 114–124
SIK 482–484
sildenafil 780, 784–786
SIN1 *see* mitogen-activated protein kinase associated protein 1
single-minded 1 (SIM1) transcription factors 147–148, 200
single-nucleotide polymorphisms (SNP) 157, 160–167, 189–194, 228, 242
SIRD *see* severe insulin-resistant diabetes
sirtuin enzymes 1164–1165
sitagliptin 492, 496, 509–510
SITAGRAMI trial 1140
skeletal disease 858–863
  bone density 390, 396, 508, 556, 793, 859–863
  diffuse idiopathic skeletal hyperostosis 858–859
  fractures 793, 859–863
  osteoporosis 793, 859–863
skeletal muscle *78*, 80, 123, 238–242
skin conditions 838–853
  acanthosis nigricans 275–276, 282, 288–290, 838–840
  achrochordons 840
  ageing 838, 841
  anti-diabetic oral agents 849–850
  bacterial infections 838–839, 845, 848
  bullosis diabeticorum 840
  calcific uraemic arteriolopathy 844
  candidal infection 845–846, 878, 881–882, 890–891
  clear-cell syringomas 847
  dermatophytosis 846
  dermopathy (shin spots) 842
  elasticity losses 838, 840
  eruptive xanthomas 841
  erythema multiforme 850
  fungal infections 838–839, 845–848, 878, 881–882, 890–891
  glucoganoma syndrome 847
  glues 838, 850
  granuloma annulare 838, 842–843, 847–848
  iatrogenic 849–850
  infections 838–840, 844–850, 878–882, 890–893
  insulin reactions 849–850
  lichen planus 846
  lower limb vascular changes 842–844
  medical device reactions 850
  metabolic factors 838–841
  nails 841, 844–849
  necrobiosis lipoidica 838–839, 842–844
  neuropathy 661–662, 848
  perforating disorders 847
  phycomyces infections 846
  pruritus 845, 847, 850
  psoriasis 838, 848–849
  recombinant insulin preparations 838, 849
  reddening 838, 843–850
  rubeosis faciei 844
  scleroedema 841
  shin spots 842
  Staphylococcus aureus 845–846, 878, 880–881
  sulfonylureas 849–850
  telangiectasia 838–839, 843–844
  thickening 838, 840–842, 848–849
  vascular changes 838–839, 842–844, 848
  vitiligo 846
  yeast infections 838–839, 845–846, 848
  yellowing 838–839, 841–843, 847
skin issues
  biopsies 661–662
  continuous glucose monitoring 451
skin tags 840
skin temperature 775
SLC30A8 genes 157, 167, 190–193
sleep 897–902
  behavioural factors 897–902, 908–910
  body weight/obesity 149–150
  cardiovascular disease 900–901
  consistency factors 898, 900
  depression 897, 899–902
  deprivation 57, 897–902
  duration problems 897–902
  hypoglycaemia 579, 584–589, 594–597
  insomnia 898–901
  mortality 900
  neuropathy 655–657, 660, 667–670, 897, 899, 901
  patterns 149–150
  physiological factors 897–902
  psychosocial aspects 908–910
  quality factors 899, 901–902
  renal function 897, 901
  restless leg syndrome 897–898
  self-management 897, 901–902
  timing problems 898, 900
  Type 1 diabetes 899, 901–902
  Type 2 diabetes 57, 899–902
sleep apnoea 898–902
Sleep Quality Index 897, 902
sleeve gastrectomy 146–147, 250, 255, 258, 554–556
slipped gastric bands 556
Slovakia 43–44
smart caps 460
smart insulins 1154, 1164
smart pens 444–446, 457
smartphones 1023–1024
smart pump therapy 431, 438, 464, 474
sMMSE *see* standardized Mini Mental Status Examination
smoking
  cancers 868
  cardiovascular disease 713, 720
  global burden of diabetes 34
  nephropathy 650
  sexual dysfunction 783, 790
SMR *see* standardized mortality ratio
snacking 372, 399, 568–569, 1006–1012
SNS *see* sympathetic nervous system
social aspects
  see also psychosocial aspects; socioeconomic status
  adolescents 1019–1031
  alcohol 956, 963–965
  behavioural factors 974–982
  body weight/obesity 142–143, 149–152
  British colonies 975
  custody 956, 962
  depression 907–918, 933–942, 945, 947–949
  determinants of diabetes 973–984
  driving 956–962
  employment 956, 961–962
  empowerment education 362
  environmental factors 973–974, 978–982
  ethnicity 973–976, 979–982
  indigenous populations 973, 976–978, 985
  inequality aspects 973–981
  insurance 956, 962–963
  isolation/support 922–923, 930–932
  leaving home factors 957, 970–971
  macro factors 973–981
  meso factors 973–975, 980–981
  obesity 142–143, 149–152, 933–952
  patient education empowerment 362
  policy aspects 973–981
  politics 974–981
  prison 956, 962
  racial aspects 973–981
  recreational drugs 957, 965–967
  sexual dysfunction 789
  stigma factors 907, 912, 917
  transition to adulthood 1019–1031
  travel 957, 967–970
  Type 2 diabetes 973–982
social cognitive theory 360
social media 1023–1024
socioeconomic status
  costs of diabetes 36–37
  cultural aspects 987–988, 991–992
  determinants of diabetes 974–976, 979–981
sodium
  children 1013
  correction 1002–1004
  depletion 334, 560, 608
  intake 369–370, 375, 423, 649, 706–708
  transport 92
sodium–glucose cotransporter 2 (SGLT-2) inhibitors 492–500, 503–504, 511–514
  adverse-effects 514
  biomarkers/precision medicine 421–422
  cancers 873
  diabetic ketoacidosis 604
  efficacy 513–514
  glucose metabolism 81–82
  heart failure 732, 738–741
  historical perspectives 17
  indications 513
  ischaemic heart disease 724–727, *729*
  microvascular complications 615–616, 619, 625–626
  modes of action 511–513
  NAFLD 820, 833–834

nephropathy 640, 644–651
pathogenesis 615–616, 619, 625–626
pharmacokinetics 513
Type 2 diabetes 70, 534–536, 539–548, 1154–1156, 1162–1164
soft tissue
fibroproliferative disorders 853–856
infections 878–879, 884–885, 891–893
SOLOIST-WHF study 546–547
soluble advanced glycation end-products 686
soluble insulin 431–436
SOLVD trial 739
somatostatin-expressing δ cells 78
somatostatinomas 305, 313–315
somatostatin (SST) 93, 304–315
sotagliflozin 546–547
SOUL 527
South Africa 61
South America 29–30, 42, 44, 46, 62
South Asia
culture/ethnicity/religion 987–997
global burden 29–31, 35
Type 1 diabetes 42
Type 2 diabetes 29–30, 56, 63–64, 67–69, 987, 990
South East Asia 29–31, 35, 42, 56, 63–64, 67–69, 1036
South Korea 845
SPACE trial 766
Spain 43, 46, 460, 1024
specialist teams 559, 562–565, 788, 1097–1105
SPICT *see* Supportive & Palliative Care Indicators Tool
spinal cord stimulation 668
SPK 482–485
SPRINT trial 1076
Src-homology-2 (SH2) B-adaptor protein-1 (SH2B1) 198
SREBP *see* sterol receptor element–binding proteins
Sri Lanka 64
SSRI *see* selective serotonin reuptake inhibitors
SST *see* somatostatin
staff composition 1103–1105
staff education 564, 573
standard deviation (SD) 452
standardized Mini Mental Status Examination (sMMSE) 923
standardized mortality ratio (SMR) 51–52
standards, in-hospital treatments 562–564
stanols 375
Staphylococcus spp. 776–777, 839, 845–846, 848, 878–881
STAR-3 study 465
starting insulin therapy 441
starvation regimes 8–10, 255–256
state of the art aspects 479–482
statins
biomarkers/precision medicine 423–425
cardiovascular disease 713–721
drug-induced diabetes 295–296, 299
global burden of diabetes 34
NAFLD 834–835
statutory driving requirements 959–961
steatosis 821–828, 832–834
Steiner, Donald 14
stem-cell therapy 1137–1143
β-cells 1137–1143
blood vessels 1140–1142
cardiovascular disease 1140–1142
definitions 1137–1138
heart failure 1140–1141
insulin replacement 1138–1140
islet cell transplantation 485, 1140
kidney disease 1142–1143
peripheral arterial disease 1140–1142
whole pancreas transplantation 485
Steno 2 trial 16, 18, 414, 616, 651–652, 670–671, 682–683, 696, 710–711
stenosing tenosynovitis 855
stenting 766–767
steroid therapies 574–575, 1091, 1093
sterol receptor element–binding proteins (SREBP) 116–119, 121, 231, 716
sterols 375
Stevens–Johnson syndrome 850
stigma factors 142, 149, 151–152, 907, 912, 917
stillbirth 1038–1039
STOP-NIDDM trial 70, 516, 537
strength, exercise 382, 384, 386, 397–398
Streptococcus pneumoniae 885–886
stress
behavioural factors 908–919
hormones 602, 608–610
hyperglycaemia 559, 564–565, 571, 574, 1001
transition to adulthood 1029
striae 309–310
strip technology 444–448
stroke 745–754
anti-platelet therapy 749, 752
atherosclerosis 745, 747–748
clinical presentation 330, 334–335
epidemiology 745–746
glycaemic management 745, 747–752
glycated haemoglobin 745, 747–749
hyperglycaemia 745, 747–753
hyperlipidaemia 745–749
hypertension 745–753
lifestyle factors 745, 752–753
management 749–753
mortality 745–746, 749–751
nitric oxide response 745, 748
pathophysiology 748
pre-diabetes 747–748
prevention strategies 745–753
primary prevention 749–750
risk factors 745–748
secondary prevention 752–753
transient ischaemic attacks 745–747, 752
structural polymorphisms 157, 160, 167
structured education support 1098–1099
structured exercise 394–396
students with diabetes 970–971
subcutaneous fat 250, 253–254
subcutaneous insulin infusion 434–442, 459–470, 565–567, 1003–1007
see also continuous subcutaneous insulin infusion
subcutaneous tissue infections 891–893
Sub-Saharan Africa 30, 44–45, 59–61
sucrose 373
Sudan 36, 45, 64, 1112
sudden cardiac death 591, 670, 740
sudoscan 663
sugar-sweetened beverages 57
suicidal ideation 35, 910, 934, 945
sulfonylureas 492–498, 501–510, 518
adverse-effects 504–505
derivatives 420
efficacy 504
gestational diabetes mellitus 1059
heart failure 742
indications 503–504
mode of action 501–503
monogenic diabetes 275–276, **278**, 282–286
nephropathy 650
pharmacokinetics 503
pregnancy 1059
skin conditions 849–850
Type 2 diabetes 537–542, 547–548
SUMMIT trial 546
superficial soft tissue infections 891–893
Supportive & Palliative Care Indicators Tool (SPICT) 1086
surgical management
body weight 146–147, 551–557
communication skills 570–571
Cushing syndrome 310–312
foot disease 771–779
historical perspectives **16**
hospitals 559–578
hyperglycaemia 559–566, 570–575
in-hospital treatment 559–578
pancreatic diseases 319–320, 326–327
peripheral vascular disease 758–760
sexual function 780, 787–788
stress hyperglycaemia 559, 564–565, 571, 574
surgical site infections 560–562, 570–571, 881, 893–894
SURPASS-4 trial 543
surrogate cell reprogramming 1147–1148
Sushrut **4**, *5*
SUSTAIN-6 trial 527, 543
Sustainable Development Goals (SDG) 1108, 1112, 1114
Sweden
cancers 867, 871
genetics 158
insulin therapy 460, 465, 467
NAFLD 828–829
obesity 258, 555
pregnancy 1035, 1044
psychological issues 908–909
Type 1 diabetes 42–47, 49–52
Type 2 diabetes 62
sweeteners 373
Switzerland 42, 483–484
symmetrical polyneuropathies 655–669
sympathetic nervous system (SNS) 129–130
sympathetic neural activation 579–588
sympathetic neuropathy 772
sympathoadrenal activation 579–588
symptomatic carotid stenosis 765–766

symptomatic peripheral arterial disease 755–756
syndromic obesities 252
syringes 435–436, 441–442
syringomas 847
system genetics 194
systemic glycaemia regulation 99–110
systemic insulin receptor substrate proteins 122
systolic blood pressure 724, 729
Systolic Hypertension in the Elderly Program (SHEP) 298

taboos and barriers 991
tacrolimus 295, 301
talk time, patient education 356
tanezumab 668–669
tanycyte cells 133–134
targeted management plans 926
target glucose concentrations 559, 561–562
taste, alteration in 338
Tattersall, Robert 12–13
T cells
  autoimmune Type 1 diabetes 203, 211, 1125–1130
  gene therapy 1148–1149
  immune modulation 1148–1149
  islet cell transplantation 487–488
  Tregs 212, 216–218, 268, 487–488, 1126–1130, 1148
  whole pancreas transplantation 487–488
TDF *see* Theoretical Domains Framework
team working *see* multidisciplinary teams
Technosphere insulin 437
TEDDY study 48–49, 210–211
teenagers *see* adolescents; transition to adulthood
T-effector cells 1126, 1128
telangiectasia 838–839, 843–844
telemedicine 999, 1004–1005, 1065, 1098, 1103
TENS *see* transcutaneous electrical nerve stimulation
teplizumab 1128–1129
testosterone 781, 784–786, 790–791
text-messaging 1023, 1027, 1030, 1065–1066, 1117
TGF-β *see* transforming growth factor β
TGR5 *see* G-protein–coupled bile acid receptors
Thailand 67, 356, 882, 1056, 1115
Theoretical Domains Framework (TDF) 361
theory of planned behaviour 359–360
therapeutic hyperinsulinaemia 579, 582–588
thermogenesis 1149–1150
thermoregulation 134–135
thiamine-responsive megaloblastic anaemia (TRMA) syndrome 288
thiazide-diuretics 295, 298–299
thiazolidinediones 493, 496–500, 506–508
  cancers 867, 872–876
  heart failure 741
  Type 2 diabetes 68–70, 157, 167, 193, 535–537, 541
thick skin 838, 840–842, 848–849
ThinkGlucose campaign 564
thirst 330–333
Thompson, Leonard 12
thrifty gene 222
thrifty genotypes 30, 158, 193–194, 222, 982
thrombolysis 750–751, 761–762
thyroid adverse events 528
thyroid disease 1016
thyroid hormones 304, 315–316
thyrotoxicosis 304, 315–316
TIA *see* transient ischaemic attacks
time-related Type 1 diabetes incidence 45–46, 48–51
timing problems, sleep 898, 900
tirzepatide 256
tissue
  see also adipose tissue
  fibroproliferative disorders 853–856
  glucose metabolism 77–82
  infections 878–879, 884–885, 891–893
  integrated insulin signalling 121–124
  selective insulins 1154, 1164
  specific insulin resistance 246–247
titrating insulin 441
TLR *see* toll-like receptor 4
TNDM *see* transient neonatal diabetes mellitus
TNF *see* tumour necrosis factor
tocilizumab 1132
TODAY study 1026–1028
toe pressure 756–757
tolbutamide 17
toll-like receptor 4 (TLR4) signalling 265–266
Tolstoi, Edward 17
topical alprostadil cream 787
topical neuropathy medications 667
topiramate 256, 553
total-body iron stores 325
total contact cast 776–778, 857
total fat mass 250–253
total iron-binding capacity 326
toxicity, insulin resistance 240–241
toxins 49–50, 57, 150–151
TRAIL 621, 681, 692, 696
tranquillizers 965
transcriptional control 118–119
transcription factor MODY 221, 275–276, 279–281
transcription factors 100, 1139–1140
  variants 157, 160, 167, 190–194, 228
transcutaneous electrical nerve stimulation (TENS) 667–668
transdermal insulin delivery 470
trans fats 374
transforming growth factor β (TGF-β) family 621
transient elastography 822–825
transient ischaemic attacks (TIA) 745–747, 752
transient neonatal diabetes mellitus (TNDM) 283–285
transition to adulthood
  acute complications 1027–1028
  adolescents 1019–1103
  anxiety disorders 1029–1030
  behavioural factors 1022–1030
  blood glucose 1019–1027
  body weight 1027–1029
  burnout 1019–1020, 1026, 1029
  care coordination 1030–1031
  chronic complications 1027–1028
  clinical management 1030
  continuous glucose monitoring 1019–1021, 1026–1027
  contraceptives 1027
  definitions 1028
  demography 1020
  depression 1029–1030
  development stages 1020–1025
  diabetic ketoacidosis 1027–1028
  distress 1029
  eating disorders 1029–1030
  education 1019–1031
  empowerment 1019, 1021–1022
  epidemiology 1020
  existing programmes/interventions 1030–1031
  family factors 1019–1031
  glycaemic levels 1020–1029
  glycated haemoglobin 1020–1031
  hyperglycaemia 1020–1025, 1028–1029
  hypoglycaemia 1020–1029
  insulin delivery 1019–1020, 1026, 1029–1031
  insulin resistance 1020–1022
  insulin therapy 1026, 1029–1031
  leaving home factors 1019–1021, 1025
  mental health 1022, 1026–1028
  nutrition 1019–1020, 1024
  physical changes 1019–1031
  pregnancy 1027
  preparation programmes 1030
  problems with 1028–1030
  psychiatric disorders 1029–1030
  psychosocial aspects 1019–1031
  self-efficacy 1019–1023, 1026–1031
  self-management 1019–1031
  social aspects 1019–1031
  stress 1029
  technology 1023–1026
  training aspects 1019–1031
  Type 1 diabetes 1019–1031
  Type 2 diabetes 1019–1020, 1023–1029
transmembrane proteins 111
transplantation
  islet cells 473–491
  nephropathy 640, 646, 648–651
  renal 1043
  whole pancreas 473–491
transsphenoidal surgery 307
transtheoretical model of change/stages 360
transurethral alprostadil 780, 787
travel 957, 967–970
treatment-induced neuropathy 658, 947
T-regulatory (Treg) cells 212, 216–218, 268, 487–488, 1126–1130, 1148
triacylglycerols *see* triglycerides
tricarboxylic acid 80, 103, 226–227, 241–242
Trichophyton rubum 846
tricyclic antidepressants 666
trigger biomarkers 211
trigger finger 855

triglycerides 79, 240–241, 713–721, 827
triple combination therapy 517–518
TrkB *see* tropomyosin-related kinase B
TRMA *see* thiamine-responsive megaloblastic anaemia
troglitazone 17
tropical calcific pancreatitis 319, 323–324
tropical chronic pancreatitis 319, 323–324
tropical diseases 35, 1108
tropomyosin-related kinase B (TrkB) 198
truncal neuropathy 658–659
tubeless patch pumps 459, 468
tuberculosis 59–61, 878–881, 885–888, 894, 1110, 1116
tumour necrosis factor (TNF)-α 265–266, 682–685, 688, 691, 1126–1128, 1132
tumour necrosis factor (TNF) apoptosis-inducing ligands 682, 692
tumour necrosis factor (TNF) ligands 621–622, 681–685, 688, 691–692
tumours 304–305, 312–317, 867, 875
Tunisia 44–45, 64
Turkey 63
Turner, Robert 17–18
twice-daily injections 431
twin cycle model 250, 254
twin studies 47–48, 159–160, 197–198
two-year-supervised resistance training **392**
Type 1 diabetes
  see also maturity-onset diabetes of the young
  adolescents 1019–1031
  age-related incidence 41–52, 204
  amylin 520, 529–530
  amyloidosis 222–223
  antigen-specific therapy 133
  anti-thymocyte globulin 1130–1131
  architecture 160
  atypical phenotypes 216–224
  autoantibodies 25, 203–212, 1125–1134
  autoimmune 25, 203–223, 1125–1136
  behavioural factors 907–919
  β-cells 203–212, 389–390, 1125–1134
  biomarkers 206–207, 211–212, 414, 418, 423, 426, 1113–1134, *1135*
  bone density 390
  cancers 390, 868, 870–871
  cardiovascular disease 383–384, 713–720
  chemical risks 49–50
  children 41–52, 203–213, 999–1016
  classification and diagnosis 23–25
  clinical presentation 330–338
  cognitive function 922–925
  current immunotherapy status 1133–1134
  diabetic ketoacidosis 216, 218, 602–608
  dietary factors 368, 371–376
  endogenous insulin secretion 438
  environmental risk factors 48–52
  epidemiology 41–54
  ethnicity 46–47
  exercise 382–390, 397–400
  familial clustering 47–48
  fractures 859
  fulminant 216–217
  gastrointestinal tract 796–798, 801–802, 807
  gene therapy 1144–1149
  genetics 45–52, 157–166, 190–194, 221–222, 1125–1126, 1144–1149
  geographic-related incidence 42–52
  global burden of 29
  heritability 159–160, 167, 191–192
  heterogeneity 158–160, 194, 1133–1134
  human leucocyte antigens 25, 41, 48, 205–213, 1125–1126
  hypertension 700–702, 705–708
  hypoglycaemia 579–587
  immunotherapies 203–223, 1125–1136
  inflammation 1126–1128, 1131–1133
  insulin 41–43, 47–51, 203–213, 384–389, 1126–1134
  ischaemic heart disease 724–728
  islet cell transplantation 473–487
  ketosis prone diabetes 217–219, 223
  latent autoimmune diabetes of adults 217–218
  LMIC care models 1108–1118
  microbe risk factors 49–51
  microbiome 261, 268–269
  mitochondrial mutations 221–222
  monitoring 404–405, 408–412
  monogenic diabetes 219–221, 275–283, 290
  mortality 51–52, 383–384, 1125
  multidisciplinary teams 1098, 1104
  nephropathy 640–652
  neuropathy 656, 659–666, 669–673
  non-insulin parenteral therapies 520, 529–530
  nutritional factors 50–51
  obesity 258
  oral health 813, 816–818
  pancreatic diseases 222–223
  pathogenesis 157–166, 190–194, 203–213, 216–224
  physical activity/exercise 382–390, 397–400
  precision medicine 414, 418, 423, 426
  pregnancy 49–51, 1034–1049, 1058–1063
  prevention strategies 383, 1126–1127
  psychosocial aspects 907–919, 922–925
  retinopathy 629, 632
  risk factors 48–52
  safety 1129–1133
  seasonal variation in diagnosis 47
  sex-related incidence 41–42, *43*, 204
  sexual dysfunction 782–783, 789–793
  sleep 899, 901–902
  specific exercise considerations 398–400
  staging 1126
  stroke 745, 749
  time-related incidence 45–46, 48–51
  toxin risks 49–50
  transition to adulthood 1019–1031
  tumour necrosis factor-α 1126–1128, 1132
  twin studies 47–48
  Type 2 diabetes differentiation 203
  vascular risk factors 389
  well-being 390
  whole pancreas transplantation 473–487
  world-wide-related incidence 42–52
  young-onset diabetes 219–221, 223
Type 2 diabetes
  adenosine triphosphate 225–226
  adolescents 1019–1020, 1023–1029
  age-related incidence **29**, 55–69, 241–242
  atherosclerotic cardiovascular disease 534, 538, 541–548
  behavioural factors 907–919
  biomarkers/precision medicine 414–426
  birth weight 57
  body weight 535–541, 547–548, 551–557, 1164
  bone density 396
  brain blood glucose 137
  cancers 396, 867–876
  candidate genes 167
  carbohydrates 534, 537
  cardiovascular disease 393–394, 534–548, 713–720
  care aims 343–352
  β-cells 13, 26, 157–158, 190–193, 225–237, 396, 1156–1160
  children 999–1004
  chronic kidney disease 534–537, 541–548, 640–652
  chronic stimulation 231–232
  classification and diagnosis 23–26
  clinical practice 534–550
  clinical presentation 137, 330–338
  cognitive function 922–927, 930
  comorbidities 534, 538, 547–548
  complications 396, 541–547
  definitions 58–59
  depression 57
  diabetic ketoacidosis 602–604
  dietary factors 240, 368–376, 1155–1156
  dipeptidyl peptidase-4 inhibitors 535, 537–542, 546–547, 1159–1160
  DNA methylation 157, 191–194
  drug-induced metabolic changes 57
  drug therapies 68–71, 1154–1166
  economic costs 68–71
  ectopic fat storage 238, 240, 245–246
  enteroendocrine cell function 266–267
  environmental risk factors 57
  epidemiology 55–73
  epigenetics 1164–1165
  ethnicity 29–30, 59–68, 987, 990, 997
  exercise 382–384, 389–400
  fasting hyperglycaemia 238, 245
  fat ingestion 227
  fetal malnutrition 57
  fractures 859–860
  gastric inhibitory polypeptides 535–540, 543, 546–547, 1156–1160
  gastrointestinal tract 796–797, 800–803, 807
  genetics 56–58, 157–194, 228–230, 250–254, 1149–1150, 1164–1165
  geographic-related incidence 55–71
  GIP 534–540, 543, 546–547
  global burden of 29–32
  GLP-1 520–530
  GLP-1RA 1154–1160, 1163–1164
  GLP-RA 534, 538–548
  glucagon-like peptides 266–268
  glucagon secretion 1160
  glucose homeostasis 128, 131–139
  glucose transport 225–228, 238–247

Type 2 diabetes (*cont'd*)
glycaemic management 393–395, 540–541, 1154–1165
glycated haemoglobin 393–395, 406, 540–541
healthcare burden 68–71
heart failure 534–538
hepatic insulin resistance 238, 242–247
heritability 157–160, 167, 191–194
heterogeneity 158–160, 194
histone modifications 157, 192–194
hyperglycaemia 71, 230–232, 238, 240–247, 534, 537–541, 548
hyperlipidaemia 230–231
hyperosmolar hyperglycaemic syndrome 602, 608–610
hypertension 700–711
hypoglycaemia 135–137, 579, 582–597
incidence 31–32, 55–71
incretins 231–232, 534, 537–548, 1154–1164
innate immune pathways 265–266
insulin action 111–112, 116–121, 124, 1154, 1160–1161
insulin deficiency 438–439
insulin resistance 238–249, 290, 438–439, 1154–1155, 1160–1162
insulin secretion 225–237, 534–540, 547–548
insulin sensitivity 534–535, 547–548
insulin therapy 438–441, 466–469, 534–548, 1154–1165
intestinal agents 1155–1156
intestinal microbiome 261–268
ischaemic heart disease 724–730
kidney disease 534–537, 541–548, 640–652
lifestyle interventions 68
linkage studies 157, 160, 167, 190
lipids 240–241, 244–245
liver 242–244
LMIC care models 1108–1118
macrophage-induced adipose tissue lipolysis 238, 245–247
maternal health 55–58, 64, 70–71
metabolic surgery 551–557
mitochondrial function 238–247
monitoring 404–412
monogenic diabetes 275–282, 285–288, 290–291
morbidity 55, 61–63, 67–68, 534, 538, 541–542, 546–548
mortality 55, 57–60, 67–68, 393
multidisciplinary teams 1097–1098, 1101–1104
muscle glycogen synthesis 238, 240–242
NAFLD 242–247, 250–254, 820–835
natural history 227–230
nephropathy 534–537, 541–548, 640–652
neuropathy 656–660, 664–665, 669–673
non-alcoholic steatohepatitis 534–537, 541–542, 546–548
non-insulin parenteral therapies 520–530
nutrition 246–247, 1164
obesity 142, 147, 150–151, 250–258
epidemiology 56–59, 62–70
future drug treatments 1164
glucose homeostasis 136
metabolic surgery 551–557
treatment in clinical practice 534–548
oral glucose lowering drugs 492–518, 534–550
oral health 813–818
pancreatic β-cells 1156–1160
pancreatic islets of Langerhans 227
pathogenesis 225–249
pathophysiology 252–254, 520, 523–524
peptides 1154–1164
pharmacogenomics 1164–1165
pharmacology 68–71, 534–548
physical activity 382–384, 389–400
PPAR 157, 167, 193, 242, 833–834, 1154–1155, 1161–1163
precision medicine 414–426, 547–548
predisposition genetics 228–230
pregnancy 55–58, 64, 70–71, 1034–1049, 1054–1066
prevention 55–56, 59–64, 67–71, 390–392
protective variants 190, **191**
protein ingestion 227
proteins 157, 160, 167, 190–194
proteomics 1164–1165
psychosocial aspects 907–919, 922–927, 930
regional patterns 59–68
remission 55, 59, 70–71, 255–258, 370–371
retinopathy 629, 634
reversal 255–258
risk factors 55–71, 240
safety 534–548, 1165
sexual dysfunction 782–783, 786, 790–793
SGLT-2 inhibitors 70, 534–536, 539–548, 1154–1156, 1162–1164
skeletal muscle 238, 240–242
sleep 57, 899–902
smart insulins 1154, 1164
social determinants 973–982
South Asian populations 29–30, 63–64, 67, 987, 990
specific exercise considerations 400
stroke 745–749
sugar-sweetened beverages 57
thiazolidinediones 68–70, 157, 167, 193, 535–537, 541
tissue selective insulins 1154, 1164
tissue-specific insulin resistance 246–247
toxin risks 57
transition to adulthood 1019–1020, 1023–1029
Type 1 diabetes differentiation 203
vascular risk factors 395
well-being 396
whole-body insulin resistance 238, 242–243, 246–247
world-wide-related incidence 55–71
tyrosine kinases 111–115, 121
tyrosine phosphorylation 114

UK *see* United Kingdom
UK Prospective Diabetes Study (UKPDS)
autoimmunity 217
β-cell failure 227
body weight 254
cardiovascular disease 349, 541, 590, 715, 725–726, 1076
care aims 348
eyes 335
glucose control 348, 646–647
glycated haemoglobin 404–406
historical aspects 3, 16–17
hyperglycaemia 682
hypertension 703, 707, 709, 711
insulin secretion 227
insulin therapy 431, 438
kidney disease 336
macrovascular complications 682–683, 689, 714
metabolic management 192
metformin 536
microvascular complications 616–617
mortality and morbidity 68
nephropathy 647, 649, 656
oral glucose-lowering agents 493–495, 501, 504
stoke 749
whole pancreas transplantation 473
ulcers, foot disease 655–663, 667–671, 771–778
Ullrich, Axel 15
ultra-long-acting insulin analogues 431, 434
ultra-rapid-acting insulin analogues 431, 434, 440
ultrasonography 316, 821–825, 828–830, 889
undiagnosed diabetes 559
unemployment 36, 65, 252, 914–915, 961–962
unfolded proteins 231, 265
United Kingdom (UK)
acute metabolic complications 603–609
adolescents 1026
body weight 147, 152, 158, 199–200
cancer 867, 872, 874
cardiovascular disease 713–714, 720
care aims 345–349
cerebrovascular disease 479, 745
children 1000
culture/ethnicity/religion 988–994
dietary factors 369–370, 373, 376
education 365
end-of-life care 1085–1089
foot disease 771–772
genetics 192, 199–200
global burden of diabetes 33–35
heart disease 725
hyperglycaemia 616–617, 682
hypoglycaemia 589–590
in-hospital treatments 559–565, 568–572
insulin therapy 465
monogenic diabetes 276–277, 281–282, 287
multidisciplinary teams 1104
NAFLD 831
National Diabetes Inpatient Audit 559, 562–564, 568
nephropathy 643–649
neuropathy 656, 667
obesity 199–200, 252, 254–255
oral anti-diabetic agents 506, 536
oral health 816, 818
pregnancy 1035–1047, 1054, 1057–1059
psychosocial aspects 917, 946–948, 951

sexual dysfunction 782, 787–788, 791–793
social aspects 957–970, 975
Type 1 diabetes 42–44, 46–48, 51–52
Type 2 diabetes 62, 68
United States of America (USA)
adolescents 1020, 1024–1027, 1030
African Americans 978–980
cancer 868
cerebrovascular disease 745–746
Diabetes Prevention Program 371, 390–392, 501, 536, 664, 979, 981, 1065, 1076
drug-induced diabetes 297–298, 301
end-of-life care 1085, 1092
epidemiology 42–46, 48
gene therapy 1145
gestational diabetes mellitus 1050–1056, 1062
global burden of diabetes 30–31, 33–36
heart failure 732–733
infections 886, 888
in-hospital treatments 559, 561–565, 570
insulin therapy 436–437, 440, 460–461, 468–470
islet cell transplantation 477, 483–484, 487
multidisciplinary teams 1092, 1100
non-insulin parenteral therapies 525–526
oral glucose lowering drugs 503, 506–508, 517
psychosocial aspects 939, 952, 957, 960–963, 975
social aspects 975–980, 988
treatments in clinical practice 535–536, 541–543, 547
Type 1 diabetes 8, 42–46
Type 2 diabetes 61–62, 67–70
universal access to care 1114, 1116, **1118**
universal screening 1056–1058
UN LMIC care models 1108, 1114
upper limbs
blood pressure 704
bone and rheumatic disorders 853–861
endocrine disorders 305
glucose monitoring 446–447
insulin therapy 435–436
ischaemia 762
lipodystrophies 290
neuropathy 656–657, 663–664, 670
skin 840–841, 846–847
upskilling of care 1098
urinary albumin excretion 350–351, 508, 620–624, 640–645, 648–650, 702, 708–709, 1043
urinary tract infections 878–881, 888–891, 894–896, 926
urine
albumin-to-creatinine ratio 640–642, 645, 649
glucose measurements 410
urogenital system 673–674
urological conditions 789
urotensin II 681, 690–692
USA *see* United States of America
ustekinumab 1132–1133

vaccinations 48–49, 878, 880, 888, 894
vacuum therapy 780, 787
VA-DT *see* Veterans Affairs Diabetes Trial
vaginal candidiasis 333, 791
VA-HIT study 715, 717
VAMP2 212
variability-grid analysis (VGA) 452
variable basal insulin delivery 461–462
variable-rate intravenous insulin infusion (VRIII) 565–566
variant interpretation, genetic sequencing 223
vascular changes, skin conditions 838–839, 842–844, 848
vascular disease
cognitive function 924–931
dementia 924–931
infections 878–894
islet cell transplantation 473, 476–487
physical activity 389, 395
risk factors 389, 395
sexual dysfunction 782
stem-cell therapy 1140–1142
Type 1 diabetes 389
Type 2 diabetes 395
whole pancreas transplantation 473, 476–487
vascular endothelial growth factors (VEGF) 621, 632, 637–638, 665
vascular reconstructions 478, 759–762
vasoactive hormones 687–690
vasoactive intestinal peptides 304, 312, 315
vasodilators 642, 688, 701, 704, 707, 740, 781
VEGF *see* vascular endothelial growth factors
Venezuela 42, 44
ventromedial nucleus 133
verbal fluency 922–930
VERIFY trial 540
vertebral artery stenosis 76, 747
VERTIS CV trial 544
very low-calorie diet (VLCD) 146, 255–256, 551–552
very low-density lipoproteins (VLDL) 246–247, 254, 424–425, 684, 705, 715–720, 727–729, 826, 832
Veterans Affairs Diabetes Trial (VA-DT) 348, 495, 682–683, 725, 729, 1076
VGA *see* variability-grid analysis
vibration-controlled transient elastography 823–824
vibration perception threshold 661
Vibrio spp. 892
Vietnam 67, 1108
vildagliptin 492, 496–497, 509–510, 540
viral infections 878, 882–886, 894
viral vectors 1144–1151
virus aetiology 210–211
visceral fat accumulation 250–254
visceral obesity 655–656, 664, 670, 673
vision
see also retinopathy
clinical presentation 333, 335–336
driving 947–949, 957
vision-threatening retinopathy 33, 629–635
visualization, continuous glucose monitoring 444, 451–454
visual perception
cognitive function 922–924, 927–930
psychosocial aspects 922–924, 927–930
vitamin C 211, 409
vitamin D 50, 409, 669–670, 993, 1133
vitamins 50, 211, 409, 650, 669–670, 993, 1133, 1155
vitiligo 846
VLCD *see* very low-calorie diet
VLDL *see* very low-density lipoproteins
vocational driving 960–961
voglibose 493, 496, 514–516
vomiting 605, 796, 802–807
von Jaeger, Eduard 8
von Mering, Josef von 7
von Noorden, Carl 8
von Recklinghausen neurofibromatosis 312, 324
VRIII *see* variable-rate intravenous insulin infusion
vulnerable population challenges 1111

Wagener, Henry 13
waist circumference 250–251, 253, 256
waist-to-hip ratio 63, 252, 375, 748, 1059, 1065
Wang Ying-lai 14
warfarin 753
wasting muscle 331–332
web-based CBT 908, 916
Weichselbaum, Anton 13
weight *see* body weight; obesity
well-being 390, 396, 907–917
Western Pacific region 29–31, 55, 65–67
West Indies 44–45
Whipple's triad 580
white adipose tissue 117–119, 122–123, 1149–1150
White, Priscilla 18–19
WHO *see* World Health Organization
whole-body insulin resistance 238, 242–243, 246–247
whole-genome sequencing 167, 211
whole pancreas transplantation 473–488
β-cell replacement 473–477, 485–488
challenges 485–488
chronic immunosuppression 487–488
clinical outcome assessments 479–481
competing therapies 482–485
enteric drainage 474
glycaemic management 473–488
grafts 473–488
historical perspectives 474
hypoglycaemia 473–484, 488
IAK 484
immunosuppression 473–488
indications 476
insulin independence 473–484
islet cell transplantation 473–491
ITA 482–485
management 473–491
morbidity 479
mortality 473, 479–483
nephropathy 473, 480, 482
neuropathy 473, 480, 482
organ source 485
outcome assessments 479–481
PAK 484
peri-procedural care 473, 485–488

whole pancreas transplantation (*cont'd*)
potential solutions 485–488
preservation 485
procedural considerations 474–476
PTA 482–485
retinopathy 480
SIK 482–484
SPK 482–485
state of the art aspects 479–481
stem-cell therapies 485
survival 473–488
tissue source 485
Type 1 diabetes 473–487
vascular disease 473, 476–487
Wilder, Russell 13, 16
Willis-Ekbom disease, sleep 897–898
Willis, Thomas 4
Wilson, Clifford 13–14
wireless pressure 805
withdrawing treatment, end-of-life care 1088, 1091–1093
within-group variability 979
Wolcott–Rallison syndrome 276, 283–284, 288
Wolfram syndrome 288
World Health Organization (WHO)
classification and diagnosis 23–25
DIAMOND Study 42–45
Innovative Care for Chronic Conditions Framework 1115
LMIC care models 1108–1118
Multinational Study of Vascular Disease in Diabetes 67
non-communicable diseases 1108–1117
world-wide-related incidence
obesity 250
Type 1 diabetes 42–52
Type 2 diabetes 55–71
wound healing 771–778

xanthomas, eruptive 839, 841
XENDOS study 257, 719

Yalow, Rosalyn 14–15
yeast infections 838–839, 845–846, 848
yellow skin/nail conditions 838–839, 841–843, 847
Young, Frank 14
young-onset diabetes 219–223, 275–277, 282, 331, 1023–1024, 1102–1103
young people, nephropathy 642

zinc-finger nucleases (ZFN) 1144
zinc insulin 16, 433
zinc transporter 8 (ZnT8) 203–204, 1126
Zuelzer, Georg 9, 11
zygomycosis (mucormycosis) 878, 884, 891

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